STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 184487

TO: Marcela Cordero Garcia
Location: REM 3A30/3C18
Art Unit: 1654
April 6, 2006

Case Serial Number: 10/802013

From: P. Sheppard
Location: Remsen Building
Phone: (571) 272-2529

sheppard@uspto.gov

Search Notes

184487

ACCESS DB # ~~[illegible]~~

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Part A

Scientific and Technical Information Center

SEARCH REQUEST FORM

Requester's Full Name: MARCELA M CORDERO GARCIA Examiner # : 80381 Date: 3/20/06

Art Unit: 1654 Phone Number: 2-2939 Serial Number: 10/802,013

Location (Bldg/Room#): RGM3A30 (Mailbox #): 3C18 Results Format Preferred (circle): PAPER DISK

****

To ensure an efficient and quality search, please attach a copy of the cover sheet, claims, and abstract or fill out the following:

Title of Invention: NOVEL CYCLOSPORINS

Inventors (please provide full names): SEE BIB D.S. (ATTCHD)

Earliest Priority Date: 3/17/03

Modified search requested 4/5/06

Search Topic:

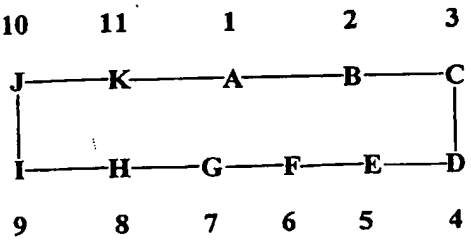
Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc., if known.

For Sequence Searches Only ***Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.***

PLEASE SRCH:

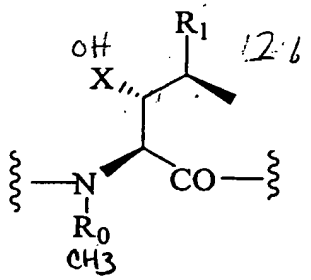
A. Chen
Rush

A compound of Formula (I):



Formula I

where A is an amino acid of Formula (II):



Formula II

and wherein:

R_0 is CH_3;

R_1 is CH=CHC(=O)Me;

X is hydroxyl;

— B is α–aminobutyric acid;

— C is a sarcosine;

D is N-methyl leucine;

E is valine;

F is an N-methyl leucine;

G is alanine;

H is D-alanine;

I is N-methyl leucine;

J is N-methyl leucine; and

K is N-methyl valine.

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=> d his ful

     (FILE 'HOME' ENTERED AT 10:29:38 ON 06 APR 2006)

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L1             STR
L21         1666 SEA SSS FUL L1
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               D IBIB ABS HITSTR L24 1-43

     FILE 'REGISTRY' ENTERED AT 11:38:26 ON 06 APR 2006
               D .SEQ SEQ3 STR L23 1-6


     FILE HOME

     FILE REGISTRY
     Property values tagged with IC are from the ZIC/VINITI data file
     provided by InfoChem.

     STRUCTURE FILE UPDATES:     4 APR 2006  HIGHEST RN 879269-14-4
     DICTIONARY FILE UPDATES:    4 APR 2006  HIGHEST RN 879269-14-4

     New CAS Information Use Policies, enter HELP USAGETERMS for details.

     TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

       Please note that search-term pricing does apply when
       conducting SmartSELECT searches.

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     *                                                          *
     * The CA roles and document type information have been removed from *
     * the IDE default display format and the ED field has been added,   *
     * effective March 20, 2005.  A new display format, IDERL, is now    *
     * available and contains the CA role and document type information. *
     *                                                          *
     ************************************************************

     Structure search iteration limits have been increased.  See HELP SLIMITS
     for details.

     REGISTRY includes numerically searchable data for experimental and
     predicted properties as well as tags indicating availability of
     experimental property data in the original document.  For information
     on property searching in REGISTRY, refer to:

     http://www.cas.org/ONLINE/UG/regprops.html

     FILE HCAPLUS

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FILE COVERS 1907 - 6 Apr 2006 VOL 144 ISS 15
FILE LAST UPDATED: 4 Apr 2006 (20060404/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate
substance identification.

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=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 11:10:23 ON 06 APR 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)
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FILE COVERS 1907 - 6 Apr 2006  VOL 144 ISS 15
FILE LAST UPDATED: 4 Apr 2006  (20060404/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> => d stat que l24
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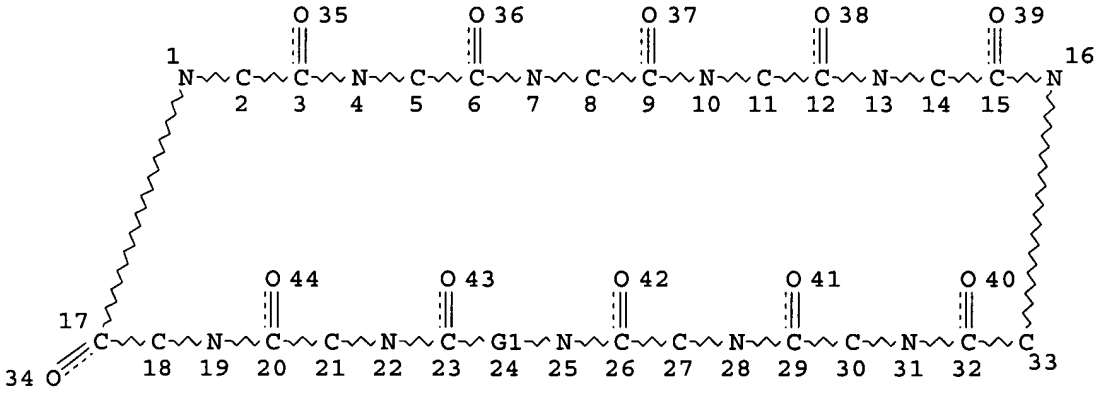

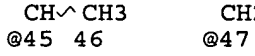


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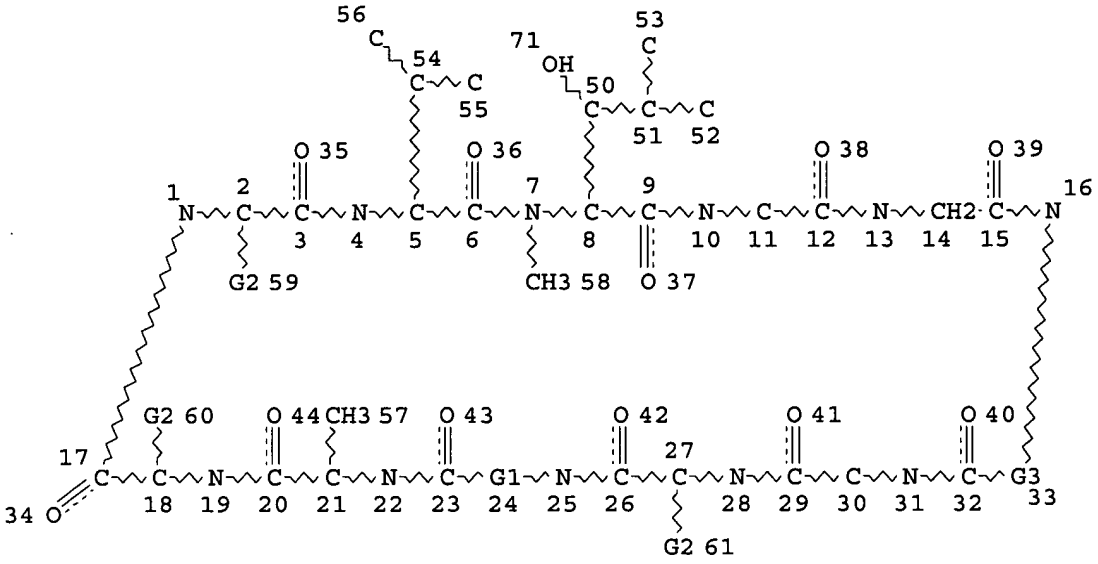

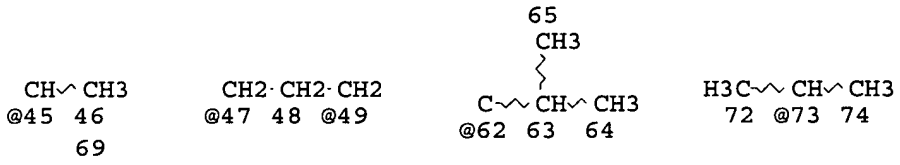

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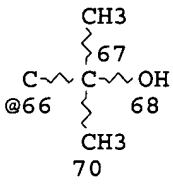

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DEFAULT ECLEVEL IS LIMITED

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NUMBER OF NODES IS 74

STEREO ATTRIBUTES: NONE
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L24 43 SEA FILE=HCAPLUS ABB=ON PLU=ON L23

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L24 ANSWER 1 OF 43 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2006:54925 HCAPLUS
DOCUMENT NUMBER: 144:164275
TITLE: Cyclosporins to treat Alzheimer's disease
INVENTOR(S): Cohen, Dalia; Gaither, Larry Alexander
PATENT ASSIGNEE(S): Novartis AG, Switz.; Novartis Pharma GmbH
SOURCE: PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006005580	A1	20060119	WO 2005-EP7556	20050712

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

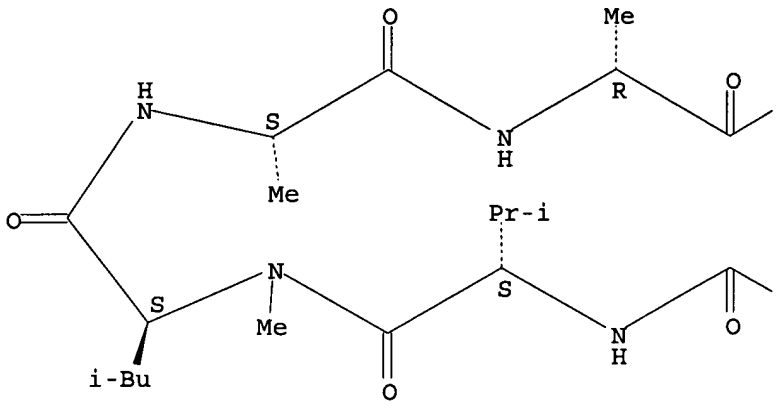
PRIORITY APPLN. INFO.: US 2004-587770P P 20040713
OTHER SOURCE(S): MARPAT 144:164275

AB Non-immunosuppressive, cyclophilin-binding cyclosporins, are useful as neuroprotective agents, e.g. in the prevention or treatment of pathol. conditions associated with Aβ secretion and/or production Examples are give for presenilin processing, analy. of carboxypeptidase (CPZ), characterization of cyclophilin D, C99 and notch cleavage, and caspase 3 activation.

IT **156047-28-8**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cyclosporins to treat Alzheimer's disease)
RN 156047-28-8 HCAPLUS
CN Cyclosporin A, 9-(N-methyl-L-valine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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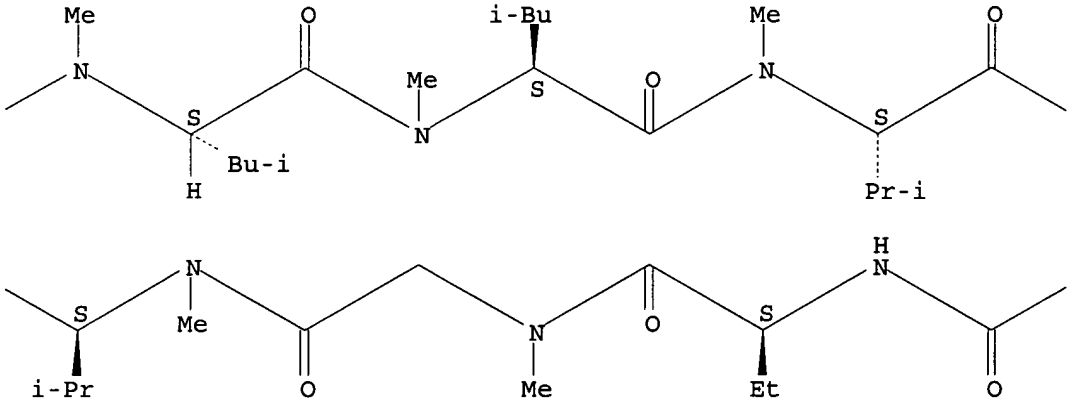

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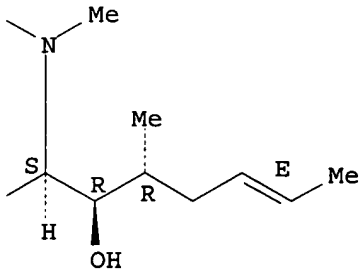


REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS

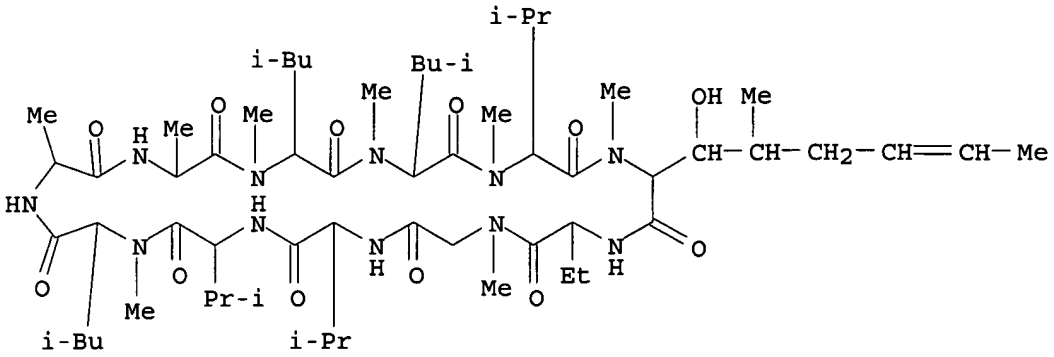
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 2 OF 43 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1210172 HCAPLUS
DOCUMENT NUMBER: 143:466194
TITLE: Oral pharmaceutical compositions containing taxanes and methods of cancer therapy employing the same
INVENTOR(S): Gutierrez-Rocca, Jose C.; Cacace, Janice L.; Selim, Sami; Testman, Robert; Rutledge, J. Michael
PATENT ASSIGNEE(S): Baker Norton Pharmaceuticals, Inc., USA
SOURCE: U.S., 14 pp., Cont.-in-part of U.S. Ser. No. 863,513, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

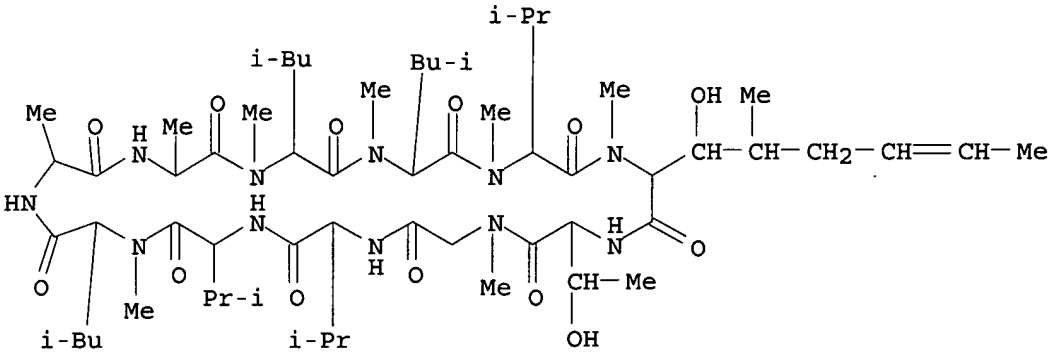
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6964946	B1	20051115	US 1998-55818	19980406
US 5968972	A	19991019	US 1996-608776	19960229
US 6245805	B1	20010612	US 1996-733142	19961016
ZA 9609001	A	19970617	ZA 1996-9001	19961025
NZ 516026	A	20030630	NZ 1998-516026	19980422
US 2005267201	A1	20051201	US 2005-165896	20050624
PRIORITY APPLN. INFO.:			US 1995-7071P	P 19951026
			US 1996-608776	A2 19960229
			US 1996-733142	A2 19961016
			US 1997-863513	B2 19970527
			US 1998-55818	A3 19980406
			NZ 1998-501127	A1 19980422

AB The present invention relates to pharmaceutical compns. for oral administration to mammalian subjects comprising a taxane or taxane derivative (e.g., paclitaxel or docetaxel) as active ingredient and a vehicle comprising at least 30% by weight of a carrier for the taxane, said carrier having an HLB value of at least about 10. The compns. may also comprise 0-70% of a viscosity-reducing co-solubilizer. The compns. may be incorporated into conventional oral pharmaceutical dosage forms, or can be in the form of a two-part medicament wherein the first part includes the taxane in a solubilizing vehicle and the second part comprises a carrier for the taxane to promote oral absorption. Methods of treatment of taxane-responsive disease conditions employing the novel compns. are also disclosed, whereby the compns. can be administered alone or in association with an oral bioavailability enhancing agent.

IT **108027-42-5**, Cyclosporin Q **108027-43-6**, Cyclosporin S
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral pharmaceutical compns. containing taxanes and methods of cancer therapy employing same)
RN 108027-42-5 HCAPLUS
CN Cyclosporin Q (9CI) (CA INDEX NAME)



RN 108027-43-6 HCAPLUS
CN Cyclosporin S (9CI) (CA INDEX NAME)



REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 3 OF 43 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:14184 HCAPLUS
DOCUMENT NUMBER: 142:120497
TITLE: Combination liposomal formulations comprising phospholipids
INVENTOR(S): Jamil, Haris; Ahmad, Imran; Ahmad, Zafeer; Anyarambhatla, Gopal
PATENT ASSIGNEE(S): Neopharm, Inc., USA
SOURCE: PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005000266	A2	20050106	WO 2004-US16413	20040522
WO 2005000266	A3	20050217		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,

LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
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RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,
SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,
SN, TD, TG

PRIORITY APPLN. INFO.: US 2003-472664P P 20030522
US 2003-495260P P 20030813

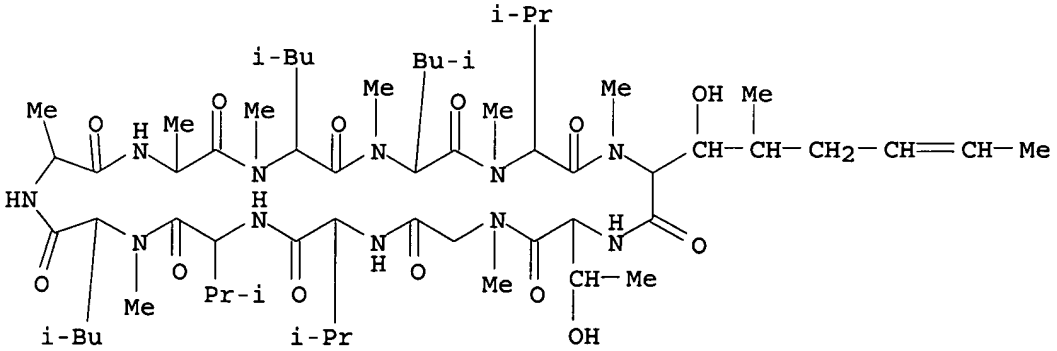
AB The present invention provides a composition comprising a physiol. acceptable carrier and two or more agents encapsulated in a liposome, wherein the combination of the two or more agents possess the following properties: (1) cytotoxicity to tumor cells, (2) nutritional properties, (3) use in application to nails, hair, skin or lips, or (4) activity against parasites and insects. The invention also provides a method of making such a composition The invention further provides a method of treating cancer when the combination of the two or more agents is cytotoxic to tumor cells. For example, an initial formulation of liposome-encapsulated paclitaxel (LEP) was prepared containing phosphatidylcholine, cholesterol and cardiolipin. Sucrose and tocopherol were added to the formulation as stabilizers in order to form a sterilized lyophilized cake. Either doxorubicin (0.5 to 1.5 mg/mL) or mitoxantrone (0.5 to 1.5 mg/mL) was dissolved in water, and the solution was employed to reconstitute the lyophilized LEP cakes. The drug to lipid ratio varied from 1:120 to 1:24 (weight/weight) for doxorubicin and 1:120 to 1:24 (weight/weight) for mitoxantrone.

The reconstitution of the LEP cake with doxorubicin or mitoxantrone solution resulted in entrapment of either of the additive drugs (doxorubicin or mitoxantrone) into the liposomal formulation of paclitaxel (LEP). Moreover, 78 to 100% of the additive drug was entrapped into the LEP at a drug to lipid ratio of 1:120 to 1:15 for mitoxantrone and 1:120 to 1:24 for doxorubicin. Presence of an addnl. drug, doxorubicin or mitoxantrone, did not alter entrapment efficiency of paclitaxel in liposomes, size or stability of liposomes. Paclitaxel content remained intact after entrapping mitoxantrone or doxorubicin. This suggested that both drugs can coexist in a single delivery system without compromising size, entrapment efficiency or stability of the liposomal formulation.

IT **108027-43-6**, Cyclosporin S
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(liposomal formulations comprising combinations of biol. active agents)

RN 108027-43-6 HCAPLUS

CN Cyclosporin S (9CI) (CA INDEX NAME)



L24 ANSWER 4 OF 43 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:626195 HCAPLUS
DOCUMENT NUMBER: 141:296284
TITLE: Synthesis and neurotrophic activity of nonimmunosuppressant cyclosporin A derivatives
AUTHOR(S): Wei, Ling; Steiner, Joseph P.; Hamilton, Gregory S.; Wu, Yong-Qian
CORPORATE SOURCE: Department of Research, Guilford Pharmaceuticals Inc., Baltimore, MD, 21224, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (2004), 14(17), 4549-4551
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 141:296284

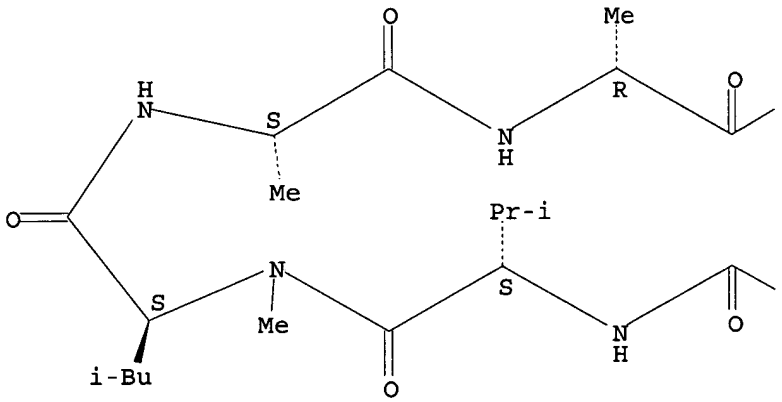
AB In order to exploit cyclophilin as a potential target for neurol. drug design, we demonstrate in this presentation that several nonimmunosuppressant analogs of cyclosporin A, modified at the various positions in the 'effector' domain, are equipotent nerve growth agents compared to cyclosporin A. Our results suggest that neurotrophic activity of cyclosporin A and its derivs. resides in the binding domain, and binding to cyclophilin and/or inhibiting rotamase activity may be a necessity for neurotrophic effects of cyclophilin ligands.

IT **156047-28-8P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis and neurotrophic activity of nonimmunosuppressant cyclosporin A derivs.)

RN 156047-28-8 HCAPLUS
CN Cyclosporin A, 9-(N-methyl-L-valine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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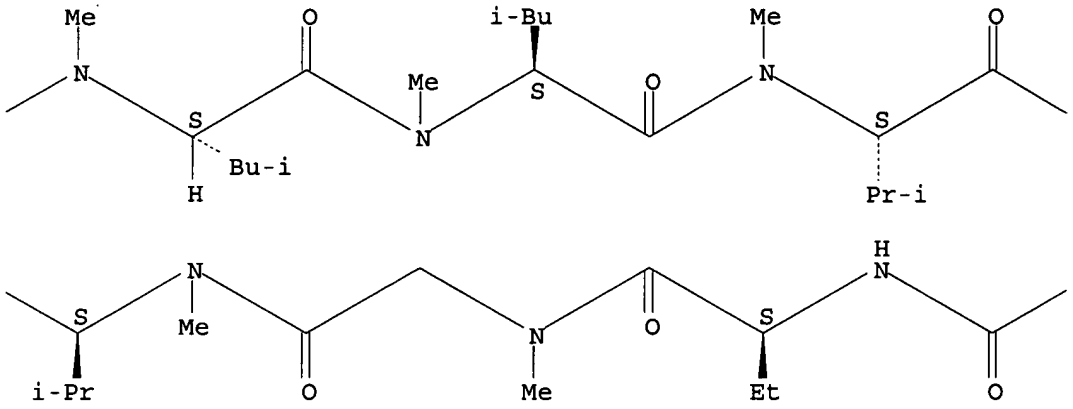

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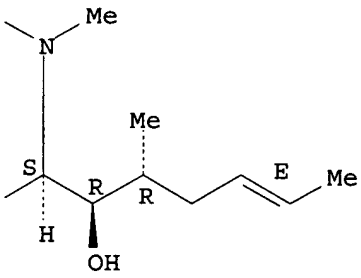

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 5 OF 43 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:80496 HCAPLUS
DOCUMENT NUMBER: 140:133858
TITLE: Paclitaxel composition for the intravesical treatment of bladder tumor and preparation method thereof
INVENTOR(S): Chung, Hesson; Jeong, Seo-young; Kwon, Ick-chan; Park, Yeong-taek; Lee, In-hyun; Kim, Se-woong; Lee, Seung-ju
PATENT ASSIGNEE(S): Korea Institute of Science and Technology, S. Korea
SOURCE: PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004009076	A1	20040129	WO 2003-KR1442	20030721
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GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS,
LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH,
PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ,
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RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
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BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2003247191	A1	20040209	AU 2003-247191 20030721
EP 1545500	A1	20050629	EP 2003-765385 20030721

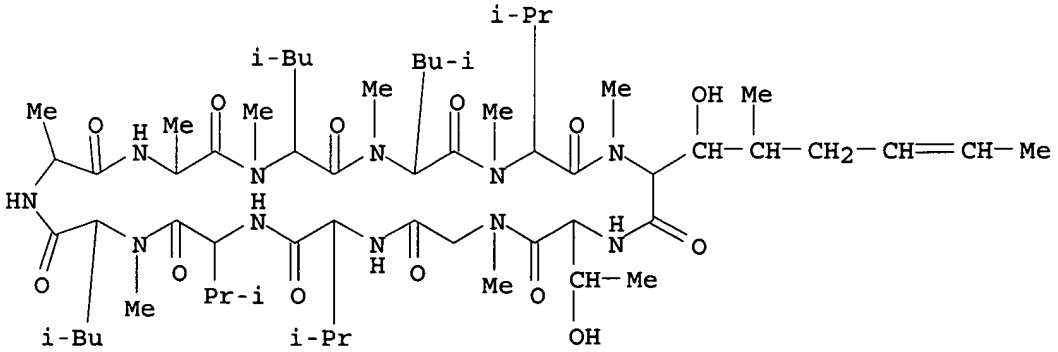
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

PRIORITY APPLN. INFO.: KR 2002-42792 A 20020720
WO 2003-KR1442 W 20030721

AB A paclitaxel composition and the preparation methods thereof for the treatment of bladder cancer wherein said paclitaxel composition comprises 4-90% by weight of at least one selected from the monoglycerides, 0.01-90% by weight of at least one oil, 0.01-90% by weight of at least one emulsifier and 0.01-20% by weight of paclitaxel. The composition of the present invention can treat bladder cancer effectively since the composition solubilizes paclitaxel, does not form aggregates, adsorbs well on the bladder wall and penetrates into the muscle layer of the bladder. Viscous oily solution was prepared by mixing completely 1 g monoolein, 0.5 g tricaprylin, and 0.3 g of Tween 80 and warmed at 40°. Paclitaxel (10.8 mg) was added into the oily solution and sonicated for complete solubilization. The composition was well dispersed in water with the average particle size of 600 nm. Paclitaxel precipitation was not observed under polarized light microscope 24 h after preparing the dispersion, and phase separation was not observed either. The above composition exists as semi-solid or solid at room temperature and in the refrigerator, resp., but as liquid at or above 40°.

IT **108027-43-6**, Cyclosporins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(paclitaxel composition for intravesical treatment of bladder tumor and preparation method thereof)

RN 108027-43-6 HCAPLUS
CN Cyclosporin S (9CI) (CA INDEX NAME)



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

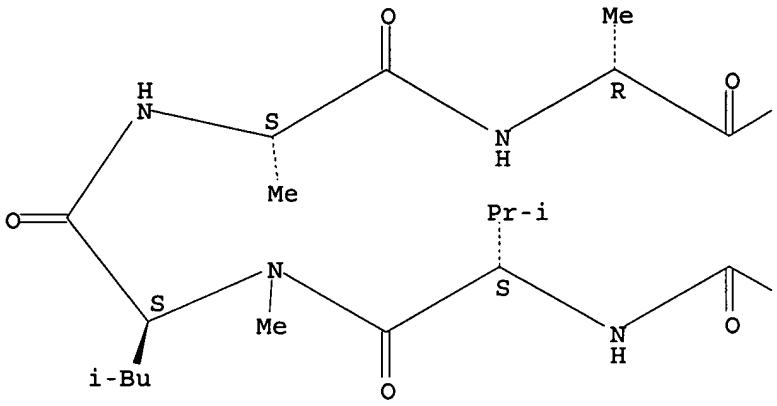
L24 ANSWER 6 OF 43 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:822514 HCAPLUS
DOCUMENT NUMBER: 140:53021
TITLE: Vasopressin Type 1A Receptor Up-regulation by Cyclosporin A in Vascular Smooth Muscle Cells Is Mediated by Superoxide
AUTHOR(S): Krauskopf, Alexandra; Lhote, Philippe; Mutter, Manfred; Dufour, Jean-Francois; Ruegg, Urs T.; Buetler, Timo M.
CORPORATE SOURCE: School of Pharmacy, Pharmacology Group, University of Lausanne, Lausanne, 1015, Switz.
SOURCE: Journal of Biological Chemistry (2003), 278(43), 41685-41690
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Based on our previous results, we investigated whether cyclosporin A (CsA)-induced vasopressin type 1A receptor up-regulation was mediated by free radicals. We report that CsA analogs with different affinities for cyclophilin and calcineurin were able to up-regulate vasopressin type 1A receptor and to generate free radicals in smooth muscle cells independently of calcineurin. Further, we demonstrate that the antioxidant N-acetyl-L-cysteine blocked the increase in vasopressin type 1A receptor mRNA and protein levels induced by CsA and that low concns. of prooxidants were able to directly increase vasopressin type 1A receptor mRNA and protein levels. In addition, short exposure to CsA or pro-oxidants was sufficient to significantly increase vasopressin type 1A receptor mRNA and protein levels. Using cell-permeable forms of superoxide dismutase and catalase, we finally show that superoxide mediates the CsA-induced effects on vasopressin type 1A receptor. These results provide strong evidence that CsA-induced superoxide generation is causally involved in vasopressin type 1A receptor expression and demonstrate for the first time that low physiol. concns. of radicals, most probably superoxide, are able to directly affect cellular signaling to increase vasopressin type 1A receptor expression in rat aortic smooth muscle cells.

IT **156047-28-8 254435-90-0**
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(vasopressin type 1A receptor up-regulation by cyclosporin A in vascular smooth muscle cells is mediated by superoxide)
RN 156047-28-8 HCAPLUS
CN Cyclosporin A, 9-(N-methyl-L-valine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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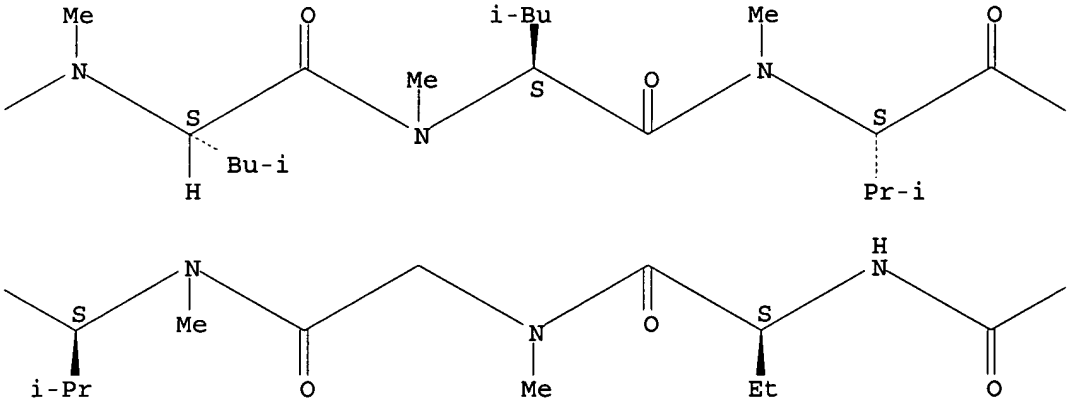

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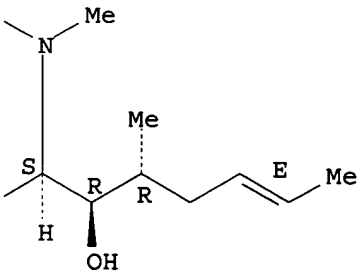
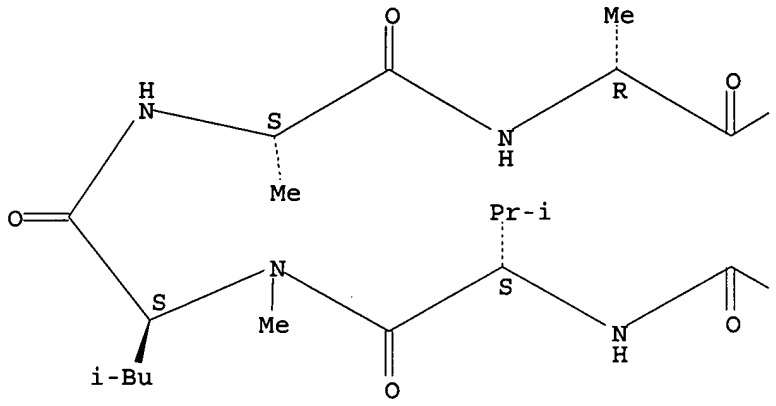


RN 254435-90-0 HCAPLUS

CN Cyclosporin A, 9-(N-ethyl-L-valine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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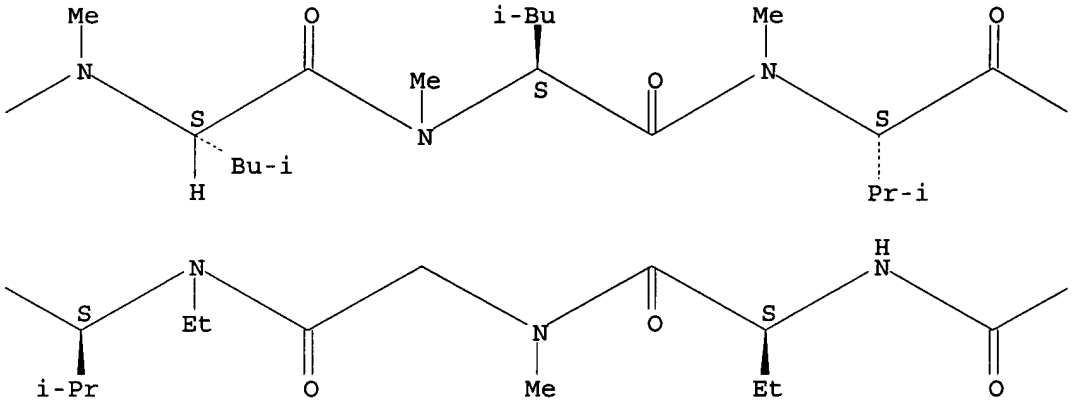

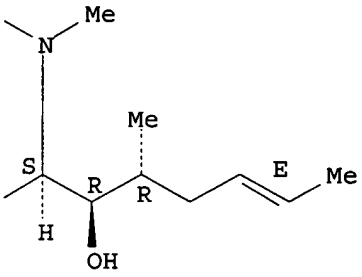

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L24 ANSWER 7 OF 43 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:496583 HCAPLUS
DOCUMENT NUMBER: 139:261550
TITLE: Synthesis and characterization of constrained cyclosporin A derivatives containing a pseudo-proline group
AUTHOR(S): Patiny, Luc; Guichou, Jean-Francois; Keller, Michael; Turpin, Olivier; Ruckle, Thomas; Lhote, Philippe; Buetler, Timo M.; Ruegg, Urs T.; Wenger, Roland M.; Mutter, Manfred
CORPORATE SOURCE: Institute of Molecular and Biological Chemistry (ICMB), EPFL-BCH, Lausanne, CH-1015, Switz.
SOURCE: Tetrahedron (2003), 59(28), 5241-5249
CODEN: TETRAB; ISSN: 0040-4020
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 139:261550

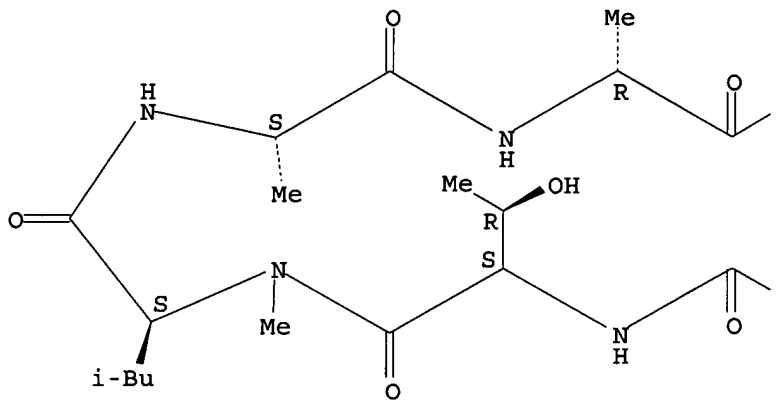
AB The chemical synthesis, conformational anal. and receptor binding studies of novel constrained cyclosporin A (CsA) analogs are described. The selective insertion of pseudo-proline (ΨPro) systems featuring different 2-C-substituents at the oxazolidine ring exerts dramatic effects upon the backbone conformation as demonstrated by NMR anal. The insertion of a ΨMeMepro at position 5 (Thr5CsA) maintains binding to cyclophilin A as well as to calcineurin and shows a 5-6 cis amide bond with all remaining amide bonds trans. The elaborated synthetic routes for generating ΨPro containing Cs derivs. pave the way for extended structure-activity relationship studies aiming at the design of potential pharmacol. active compds. with a selective activity profile.

IT **603973-23-5P 603973-24-6P**
RL: PAC (Pharmacological activity); PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(synthesis, conformational anal. and receptor binding studies of constrained cyclosporin A derivs. containing pseudo-proline group)

RN 603973-23-5 HCAPLUS
CN Cyclo[L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl-(2S,3R,4R,6E)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoyl-(2S)-2-aminobutanoyl-N-methylglycyl-N-ethyl-L-valyl-L-threonyl-N-methyl-L-leucyl] (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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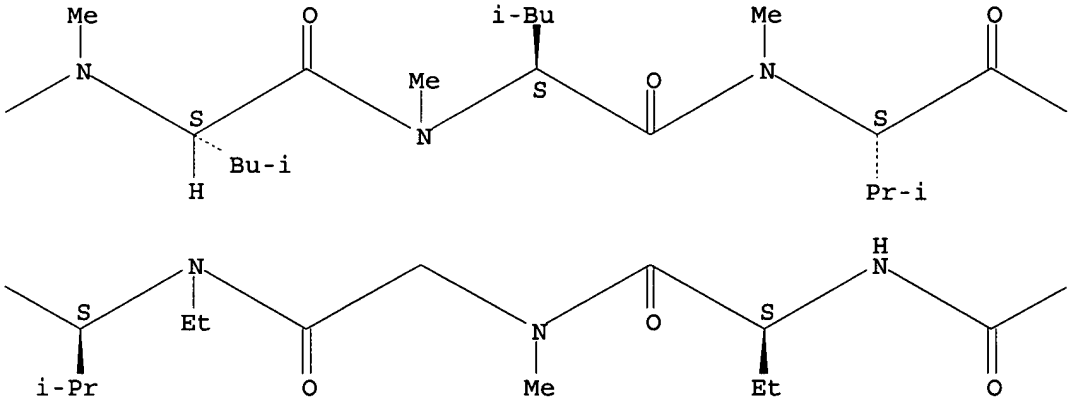

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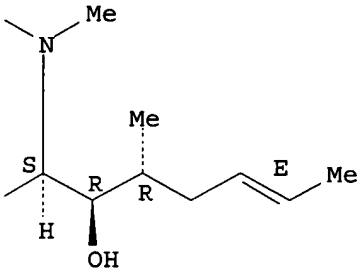
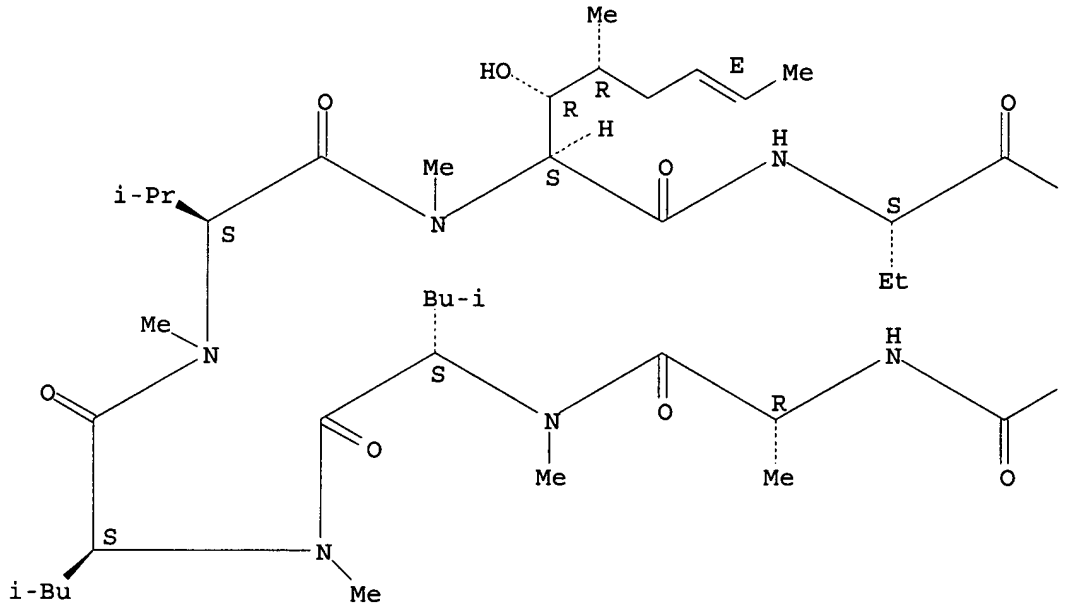


RN 603973-24-6 HCAPLUS
CN Cyclo[L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl-(2S,3R,4R,6E)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoyl-(2S)-2-aminobutanoyl-N-methylglycyl-N-ethyl-L-valyl-(4S,5R)-5-methyl-2-phenyl-4-oxazolidinecarbonyl-N-methyl-L-leucyl] (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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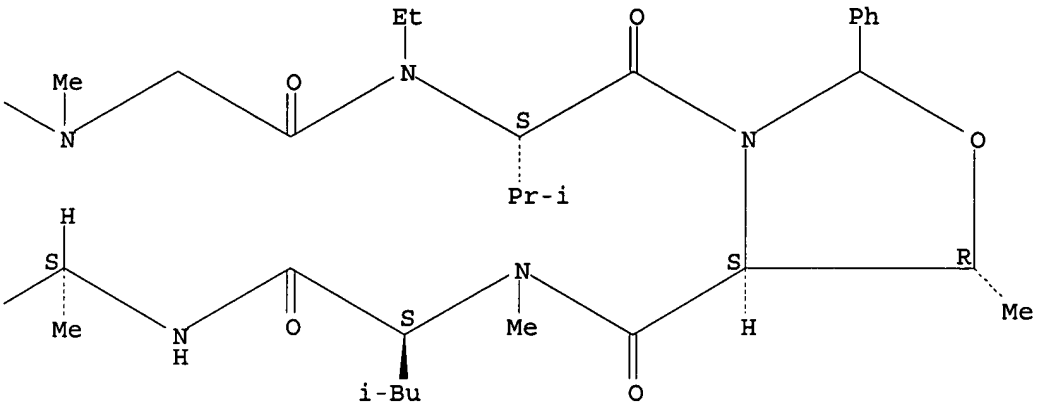

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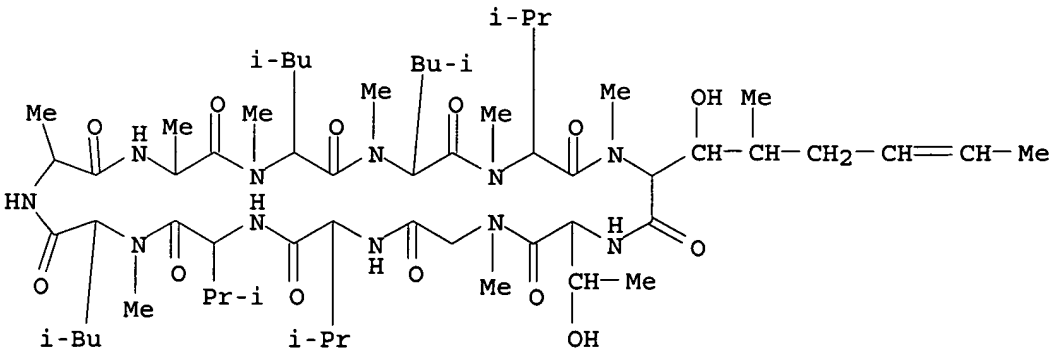
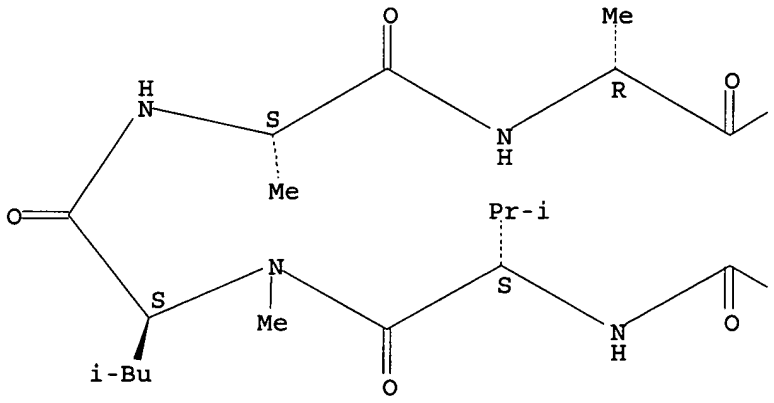
L24 ANSWER 8 OF 43 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:214417 HCAPLUS
DOCUMENT NUMBER: 138:221831
TITLE: Solution conformations of tripeptides and cyclosporins using vibrational circular dichroism and computational methods
AUTHOR(S): Bodack, Louise Ann
CORPORATE SOURCE: Syracuse Univ., Syracuse, NY, USA
SOURCE: (2001) 275 pp. Avail.: UMI, Order No. DA3055958
From: Diss. Abstr. Int., B 2002, 63(6), 2852
DOCUMENT TYPE: Dissertation
LANGUAGE: English
AB Unavailable
IT **108027-43-6**, Cyclosporins
RL: PRP (Properties)
(solution conformations of tripeptides and cyclosporins using vibrational CD and computational methods)
RN 108027-43-6 HCAPLUS
CN Cyclosporin S (9CI) (CA INDEX NAME)



L24 ANSWER 9 OF 43 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:692278 HCAPLUS
DOCUMENT NUMBER: 138:271939
TITLE: New synthetic routes to NEtXaa4-cyclosporin derivatives as potential anti-HIV drugs
AUTHOR(S): Muamba, T.; Hubler, F.; Guichou, J.-F.; Patiny, L.; Rueckle, T.; Brunner, L.; Wenger, R.; Mutter, M.
CORPORATE SOURCE: Institute of Organic Chemistry, University of Lausanne, Lausanne, CH-1015, Switz.
SOURCE: Peptides: The Wave of the Future, Proceedings of the Second International and the Seventeenth American Peptide Symposium, San Diego, CA, United States, June 9-14, 2001 (2001), 130-131. Editor(s): Lebl, Michal; Houghten, Richard A. American Peptide Society: San Diego, Calif.
CODEN: 69DBAL; ISBN: 0-9715560-0-8
DOCUMENT TYPE: Conference
LANGUAGE: English
AB A symposium report. NEtXaa4CsA derivs. (NEtXaa = Nα-ethylamino acid; CsA = cyclosporin A) were synthesized and their biol. activities were studied. The results indicate that the cyclosporin N-Et derivs. show comparable binding affinities but strongly reduced immunosuppressive activities compared to CsA itself.
IT **254435-90-0P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and anti-HIV activity of N-ethylamino acid-containing cyclosporin-A derivs.)
RN 254435-90-0 HCAPLUS
CN Cyclosporin A, 9-(N-ethyl-L-valine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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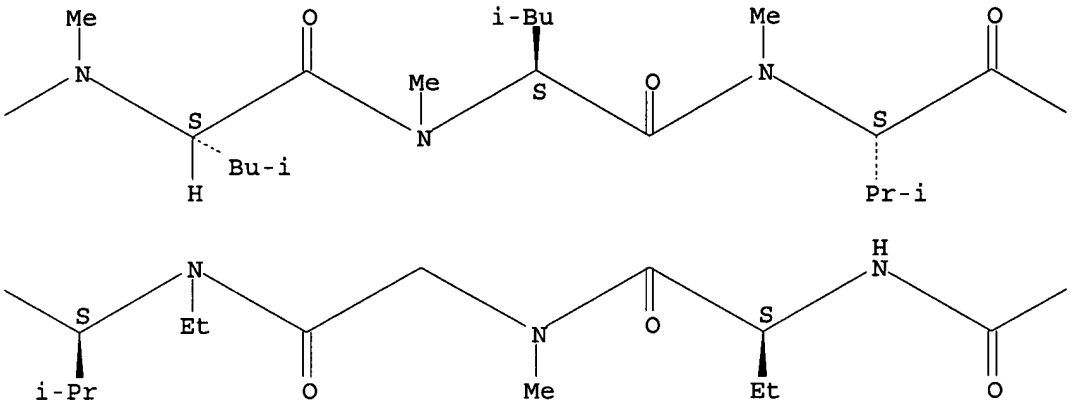

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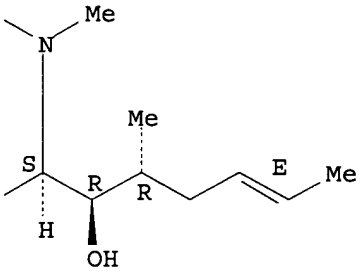


REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

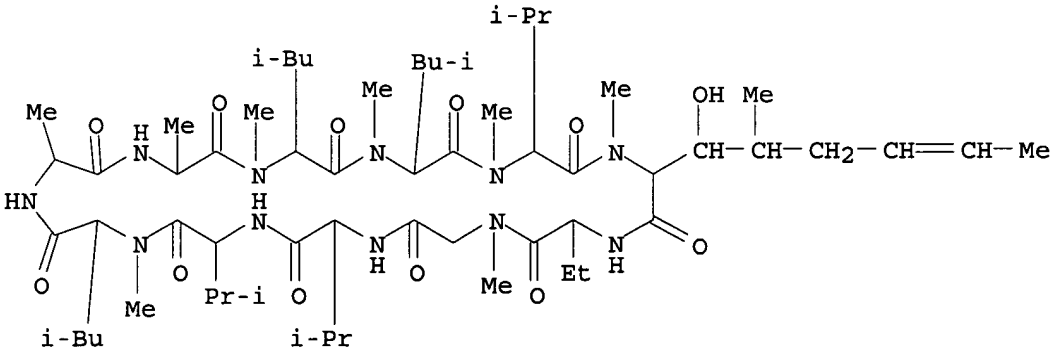
L24 ANSWER 10 OF 43 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:688784 HCAPLUS
DOCUMENT NUMBER: 137:345609
TITLE: Cyclosporins: Structure-Activity Relationships for the Inhibition of the Human FPR1 Formylpeptide Receptor
AUTHOR(S): Loor, Francis; Tiberghien, Francoise; Wenandy, Tom; Didier, Agnes; Traber, Rene
CORPORATE SOURCE: Strasbourg 1 University, Strasbourg, F-67083, Fr.
SOURCE: Journal of Medicinal Chemistry (2002), 45(21), 4613-4628
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The human formylpeptide receptor (FPR) is a seven-transmembranous G-protein-coupled receptor (7TM-GPCR) for chemotactic peptides of bacterial origins, possibly involved in the recruitment and activation of neutrophils in various inflammatory diseases of mucosal epithelia. Mutational analyses suggest that interactions of formylated peptides with

FPR occur on the outer exoplasmic leaflet/domains of the plasma membrane. The immunosuppressive and antifungal antibiotic cyclic undecapeptide cyclosporin A (CsA; cyclo-[MeBmt1-Abu2-MeGly3-MeLeu4-Val5-MeLeu6-Ala7-D-Ala8-MeLeu9-MeLeu10-MeVal11]) and some tested analogs such as [Ala2]-CsA, [Thr2]-CsA, [Val2]-CsA, and [Nva2]-CsA were able of inhibiting the binding of formylpeptides to the FPR, with [D-MeVal11]-CsA (CsH) being much more active than the other analogs. CsH is devoid of immunosuppressive and antifungal activities, and its large potency for human FPR inhibition is of inverse agonism origin. Formylpeptide binding to FPR-expressing cells does not only induce chemotaxis; it also causes a rapid release of granule enzymes in the extracellular medium, allowing the easy monitoring of any inhibition of FPR function "in vivo" (with intact live cells). With such an assay, CsH was confirmed to be the most potent FPR inhibitory cyclosporin, although a far related immunosuppressive cyclosporin analog, FR901459 ([Thr2, Leu5, Leu10]-CsA), was found to display a high FPR inhibitory activity (FPR-InhA). To establish structure-activity relationships (SAR) for FPR function inhibition, 59 cyclosporins were now studied by this standardized assay (with differentiated human leukemic cell line HL-60 as FPR-expressing cells and with N-acetyl-β-D-glucosaminidase release as read-out). These SAR confirmed the low FPR-InhA of classical cyclosporins, where such activity was only seldom found: the most active ones ([Thr2, Ile5]-CsA, [aMeIle11]-CsA, and [MeAla11]-CsA) remained 3-10-fold less potent than CsH. In contrast, the SAR disclosed that N10-desmethylated cyclosporins were particularly prone to display a large FPR-InhA: their most potent one was a [Thr2, Gly3, Leu5, D-Hiv8, Leu10]-CsA, found to be only 2-4-fold less active than [D-MeVal11]-CsA (CsH), with which it shows six differences out of 11 residues. Because the free conformations of both CsH and N10-desmethylated cyclosporins differ from those of "classical" (N10-methylated, [L-MeVal11]-using) cyclosporins, these potent FPR inhibitory cyclosporins probably bind to FPR pharmacophores for which classical cyclosporins show little affinity. Moreover, because the conformations of the N10-desmethylated cyclosporins widely differ from the CsH one, they probably bind to different pharmacophores on the FPR mols.

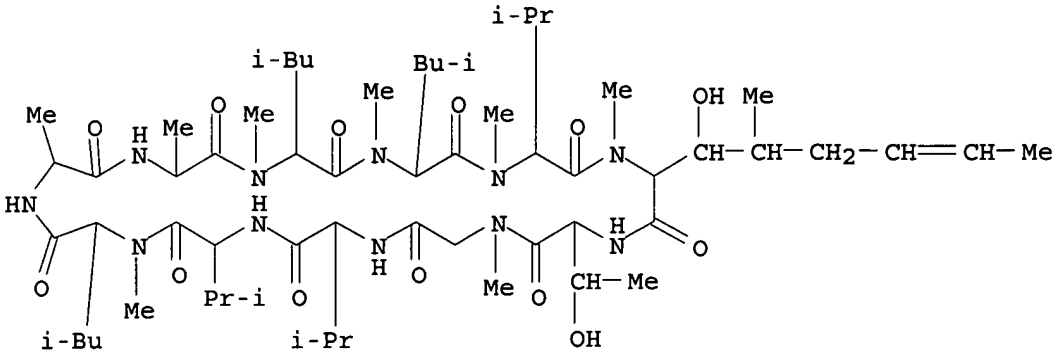
IT **108027-42-5**, Cyclosporin Q **108027-43-6**, Cyclosporin S **156047-28-8**
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cyclosporins structure-activity relationships for inhibition of human FPR1 formylpeptide receptor)

RN 108027-42-5 HCAPLUS
CN Cyclosporin Q (9CI) (CA INDEX NAME)



RN 108027-43-6 HCAPLUS

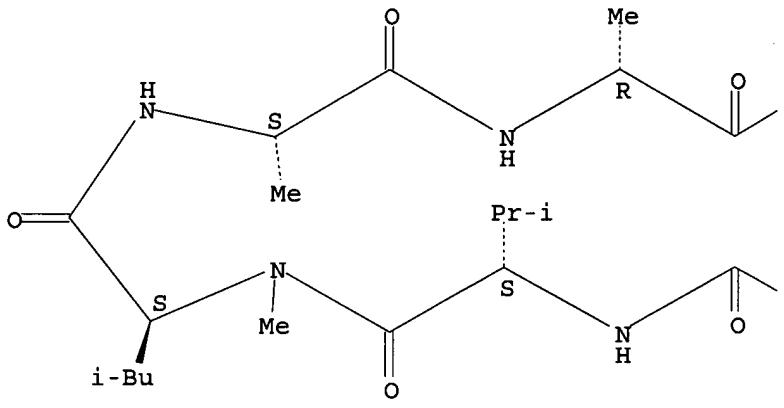
CN Cyclosporin S (9CI) (CA INDEX NAME)



RN 156047-28-8 HCAPLUS
CN Cyclosporin A, 9-(N-methyl-L-valine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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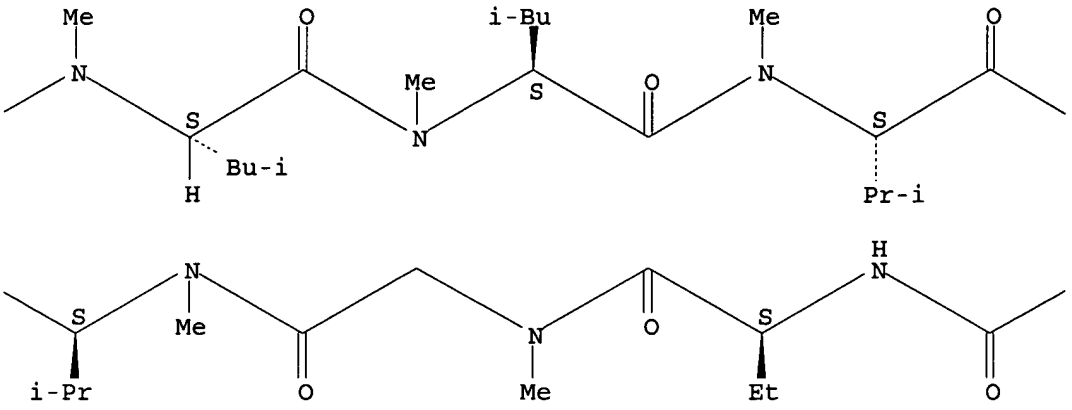

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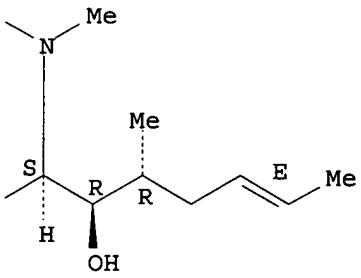


REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

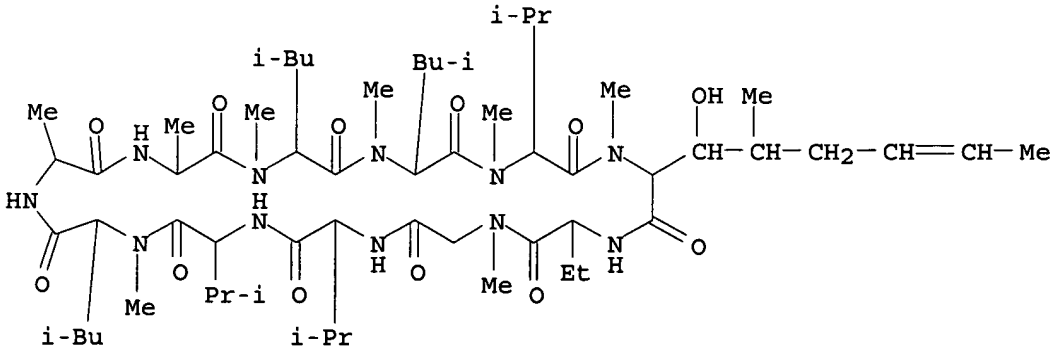
L24 ANSWER 11 OF 43 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:688783 HCAPLUS
DOCUMENT NUMBER: 137:362480
TITLE: Cyclosporins: Structure-Activity Relationships for the Inhibition of the Human MDR1 P-Glycoprotein ABC Transporter
AUTHOR(S): Loor, Francis; Tiberghien, Francoise; Wenandy, Tom; Didier, Agnes; Traber, Rene
CORPORATE SOURCE: Strasbourg 1 University, Strasbourg, F-67083, Fr.
SOURCE: Journal of Medicinal Chemistry (2002), 45(21), 4598-4612
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cyclic undecapeptide cyclo-[MeBmt1-Abu2-MeGly3-MeLeu4-Val5-MeLeu6-Ala7-D-Ala8-MeLeu9-MeLeu10-MeVal11], the immunosuppressive and antifungal antibiotic cyclosporin A (CsA), was reported to interfere with the MDR1 P-glycoprotein (Pgp), a transmembranous ATP binding cassette (ABC)

transporter with phospholipid flippase or "hydrophobic vacuum cleaner" properties that mediate multidrug resistance (MDR) of cancer cells. By use of photoaffinity-labeled cyclosporins and membranes from Pgp-expressing cells, it was recently shown that in vitro, Pgp mols. could bind a large cyclosporin domain involving residues 4-9 as well as the side chain of residue 1. Tumor cell MDR can also be reversed by a product more distantly related to cyclosporin with the structure [Thr2, Leu5, D-Hiv8, Leu10]-CsA (SDZ 214-103). In a standardized assay that measures Pgp function in vivo (on intact live cells) by the Pgp-mediated efflux of the calcein-AM Pgp substrate and uses human lymphoblastoid MDR-CEM (VBL100) cells as highly resistant Pgp-expressing cells, SDZ 214-103 was one of the most active Pgp inhibitors among naturally occurring cyclosporins, with an IC50 of 1.6 μM in an assay where CsA gives an IC50 of 3.4 μM. Using the in vivo assay, 60, mostly natural, cyclosporin analogs were analyzed to establish structure-activity relationships (SAR). Our SAR are compatible with the in vitro-defined Pgp binding domain model and further disclose that in vivo Pgp inhibition is favored by larger hydrophobic side chains on cyclosporin residues 1, 4, 6, and 8 and a smaller one on residue 7, although with no effect on the residue 5 side chain; moreover, larger hydrophobic side chains on other residues 2, 3, 10, and 11 (outside the in vitro-defined Pgp binding domain) also favor the eventual inhibition of Pgp function. The N-desmethylation of any of the seven N-methylated amides, as naturally occurring in numerous cyclosporins, regularly leads to a decreased Pgp inhibitory activity (Pgp-InhA), up to its abrogation if it occurs at residues 4 and 9. Nevertheless, despite unfavorable use of [Thr2] and [Leu10] residues, all [D-Hiv8] analogs whose lead is SDZ 214-103 show a large Pgp-InhA. The SAR for Pgp inhibition by cyclosporins are thus very complex. Because CsA and SDZ 214-103 show largely different conformations when free in solution, but remarkably similar ones when bound to the cytosolic cyclophilins, SAR for Pgp inhibition must similarly include requirements for occurrence of suitable conformers for insertion in the cell membrane, sufficient conformational plasticity for gaining access to Pgp binding sites, and an adequate conformer structure there to achieve such binding with a high enough affinity and possibly escape from sequestration on cyclophilins.

IT **108027-42-5**, Cyclosporin Q **108027-43-6**, Cyclosporin S **156047-28-8**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of the human MDR1 P-glycoprotein ABC transporter by cyclosporin analogs and structure activity relationships)

RN 108027-42-5 HCAPLUS

CN Cyclosporin Q (9CI) (CA INDEX NAME)



RN 108027-43-6 HCAPLUS
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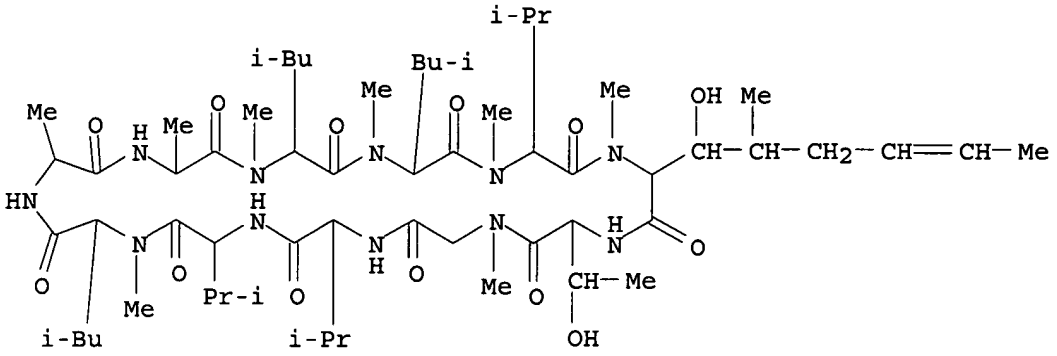
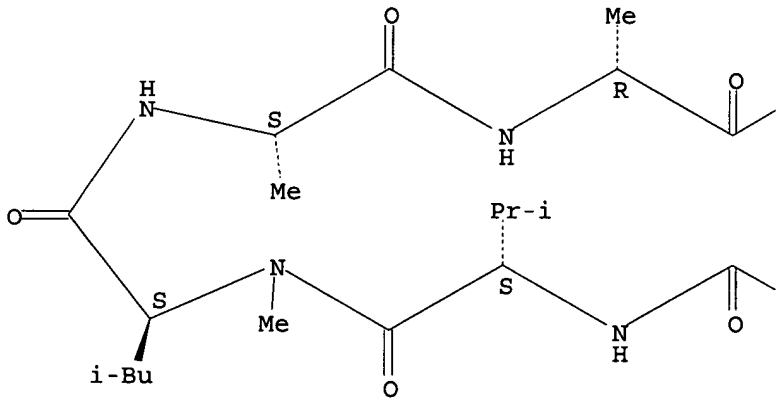


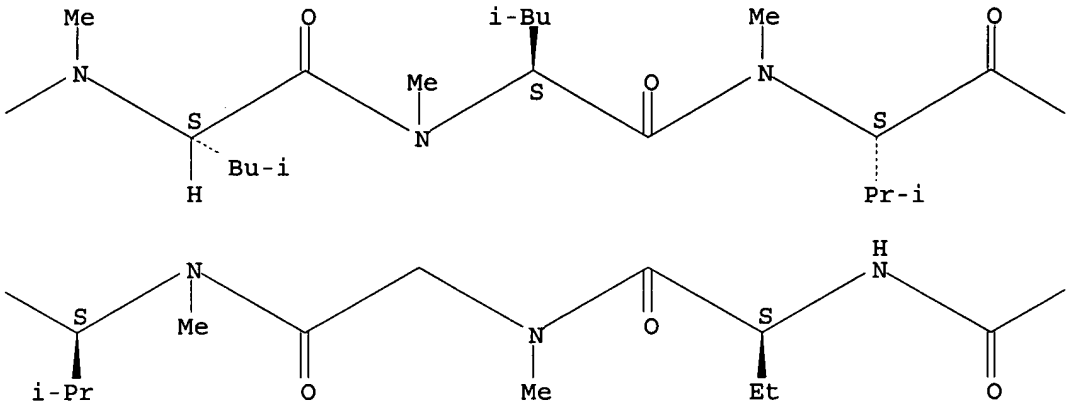
RN 156047-28-8 HCAPLUS
CN Cyclosporin A, 9-(N-methyl-L-valine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



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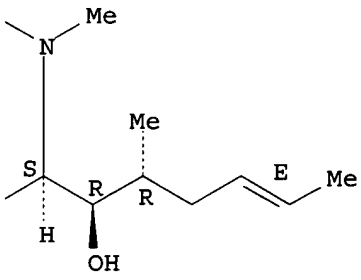


REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

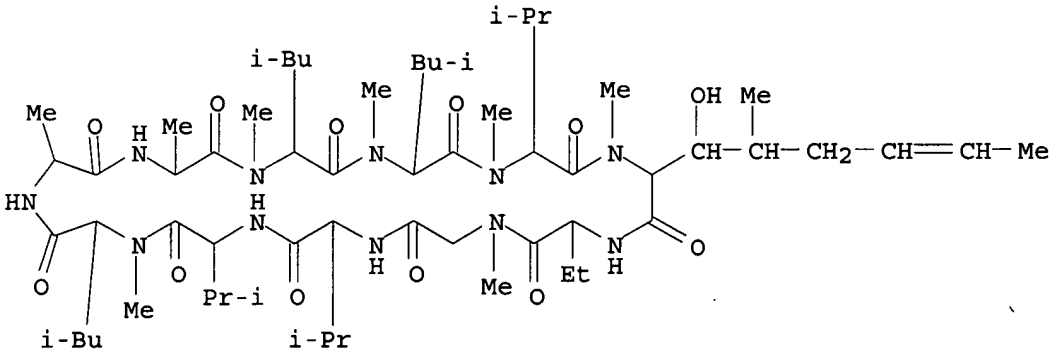
L24 ANSWER 12 OF 43 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:508609 HCAPLUS
DOCUMENT NUMBER: 135:257447
TITLE: Spontaneous N → O acyl shift in the [M + H]+ ions of [MeBmt1]-cyclosporins in an ion trap
AUTHOR(S): Jegorov, Alexandr; Havlicek, Vladimir
CORPORATE SOURCE: Galena Co., Ceske Budejovice, 370 05, Czech Rep.
SOURCE: Journal of Mass Spectrometry (2001), 36(6), 633-640
CODEN: JMSPFJ; ISSN: 1076-5174
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In an ion trap the protonated mols. of the cyclic undecapeptides cyclosporins having 3-hydroxy-4-methyl-2-methylamino-6-octenoic acid (MeBmt) in their backbone undergo an N → O peptidyl shift into the corresponding [M + H]+ ions of isocyclosporins. This rearrangement does not take place in cyclosporins [Bmt1]Cs and [3'-deoxy-MeBmt1]Cs. In cyclosporin [Thr2]Cs having two threonines in the mol., only one of them participates in the N,O-acyl transfer. It can be concluded that the

presence of the basic N-methylamino group of MeBmt, which can serve as the primary site of protonation, is necessary for isocyclosporin formation. A dominating ion series originating from the primary cleavage between MeBmt (first position in the cyclosporin ring) and amino acid residue at the neighboring eleventh position is then observed in collision-induced dissociation spectra of protonated mols. of cyclosporins. This "isocyclosporin" ion series can effectively be used for easy and complete cyclosporin sequencing using a tandem mass spectrometric (MS3) experiment in an ion trap. The paper further introduces an improved Gross mass spectral nomenclature for cyclic peptide sequencing and several techniques for the generation of protonated mols. of cyclosporins. Their preparation represents the fundamental requirement for smooth sequencing of cyclosporins by tandem mass spectral techniques.

IT **108027-42-5**, Cyclosporin Q
RL: PRP (Properties)
(amino acid sequencing of cyclosporins using isocyclosporin structures generated by N→O acyl shifts in ion traps during CID)

RN 108027-42-5 HCAPLUS
CN Cyclosporin Q (9CI) (CA INDEX NAME)



REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 13 OF 43 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:380357 HCAPLUS
DOCUMENT NUMBER: 134:371585
TITLE: Nonimmunosuppressive cyclosporin A derivative for hair growth
INVENTOR(S): Kim, Sang Nyun; Ahn, Ho Jeong; Kim, Myung Kee; Kim, Jong Il; Kim, Jung Hun; Lee, Chang Woo; Lee, Min Ho; Kim, Chang Deok; Cho, Ho Song; Kim, Hyun Sik; Jung, Min Hwan; Kim, Seung Jin
PATENT ASSIGNEE(S): Lg Chemical Co., Ltd., S. Korea
SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001035913	A1	20010525	WO 2000-KR1281	20001109

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

KR 2001049236	A	20010615	KR 2000-14837		20000323
US 6521595	B1	20030218	US 2000-580694		20000530
CA 2380362	AA	20010525	CA 2000-2380362		20001109
CA 2380362	C	20040420			
EP 1229889	A1	20020814	EP 2000-978090		20001109
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
BR 2000014635	A	20021001	BR 2000-14635		20001109
AU 760013	B2	20030508	AU 2001-15583		20001109
PRIORITY APPLN. INFO.:			KR 1999-51646	A	19991119
			KR 2000-14837	A	20000323
			WO 2000-KR1281	W	20001109

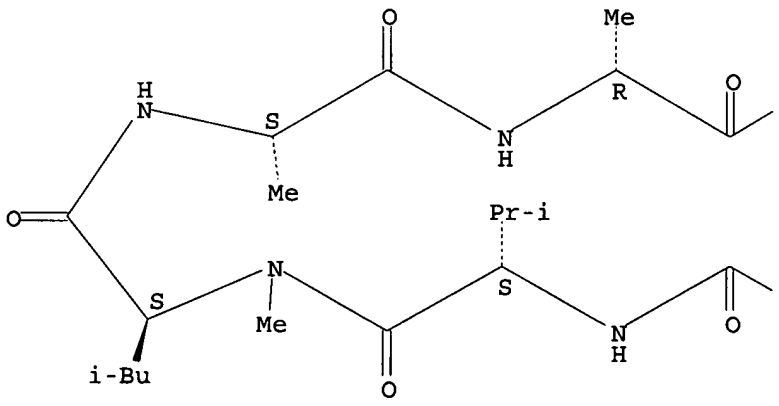
AB The present invention relates to agents for treating alopecia and stimulating hair growth comprising an active ingredient of nonimmunosuppressive [γ-hydroxy-N-methyl-L-leucine4]cyclosporin A (I) having superior hair growth-promoting effect, wherein the hydroxyl group is added to the γ carbon position of No.4 N-methyl-L-leucine of cyclosporin A by the microorganism. Thus, a hair tonic was prepared from EtOH 40.0, I 0.1, tocopherolacetic acid 0.1, salicylic acid 0.3, L-menthol 0.3, Tween-20 0.5, perfume and dye qs and water to 100%. I was obtained from Sebekia benihana culture. I not only had much lower degree of immunosuppression but also maintained superior hair growth effects to the nontransformed cyclosporin A.

IT **156047-28-8P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses)
(nonimmunosuppressive cyclosporin A derivative for hair growth)

RN 156047-28-8 HCAPLUS
CN Cyclosporin A, 9-(N-methyl-L-valine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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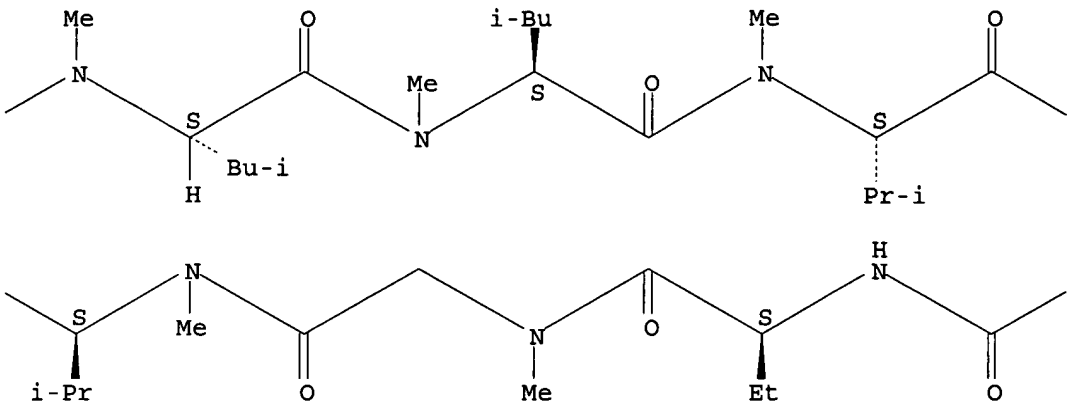

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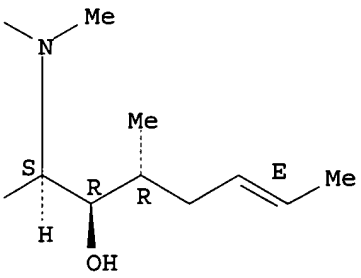


REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 14 OF 43 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:319777 HCAPLUS
DOCUMENT NUMBER: 134:344591
TITLE: Method and compositions for administering taxanes orally to human patients
INVENTOR(S): Brodor, Samuel; Duchin, Kenneth; Selim, Sami
PATENT ASSIGNEE(S): Baker Norton Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001030448	A1	20010503	WO 2000-US29633	20001027

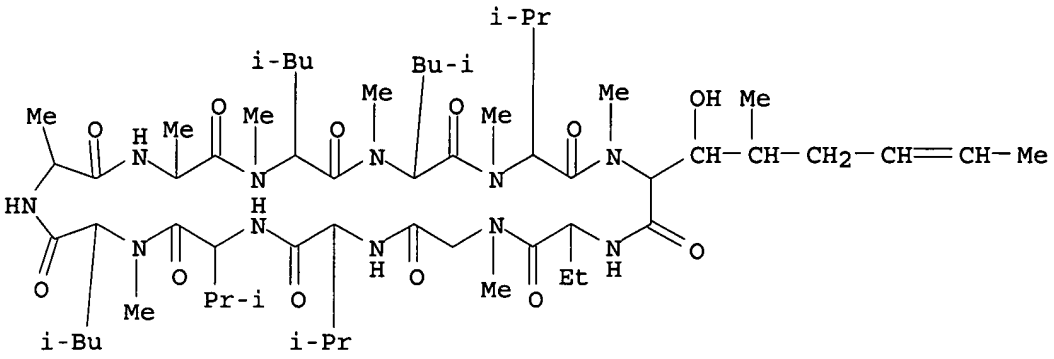
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2389583	AA	20010503	CA 2000-2389583		20001027
EP 1225956	A1	20020731	EP 2000-972373		20001027
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL					
BR 2000015149	A	20021029	BR 2000-15149		20001027
JP 2003512443	T2	20030402	JP 2001-532859		20001027
NO 2002002008	A	20020619	NO 2002-2008		20020426
ZA 2002003358	A	20030429	ZA 2002-3358		20020426
PRIORITY APPLN. INFO.:			US 1999-162310P	P	19991027
			WO 2000-US29633	W	20001027

AB Taxane antineoplastic agents which exhibit poor or non-existent oral bioavailability are administered orally to human patients suffering from taxane-responsive disease conditions and made sufficiently bioavailable to achieve therapeutic blood levels. In a preferred embodiment, the taxane, preferably paclitaxel, is co-administered to the patient with an oral cyclosporin as bioavailability-enhancing agent, preferably cyclosporin A (CyA). The maximum effect of CyA on the enhancement of the exposure to paclitaxel was observed at a single dose of CyA of 15 mg/kg. By one preferred method, a dose of oral enhancer is administered about 0.5-72 h before the taxane and a second dose of the enhancer is administered immediately before, together with or immediately after the taxane. A method of treating human patients suffering from taxane-responsive disease conditions is also provided, as well as a method for providing such treatment while preventing or reducing hypersensitivity and allergic reactions without the need for premedication. For example, a male patient with prostate cancer received an enhancer (Sandimmune, 5 mg/kg in two doses, 1 h apart). Just after the 2nd dose, the patient drank a Cremophor EL/alc.-based solution of paclitaxel in a dose of 2 mg/kg. Plasma levels of 0.05 μM of paclitaxel were present for about 10-12 h after oral administration of paclitaxel, i.e. levels comparable to those found in breast cancer patients receiving 96-h i.v. infusion of paclitaxel.

IT **108027-42-5**, Cyclosporin Q **108027-43-6**, Cyclosporin S
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cyclosporin derivs. for enhancement of oral bioavailability of antitumor taxanes in human patients)

RN 108027-42-5 HCAPLUS
CN Cyclosporin Q (9CI) (CA INDEX NAME)



RN 108027-43-6 HCAPLUS
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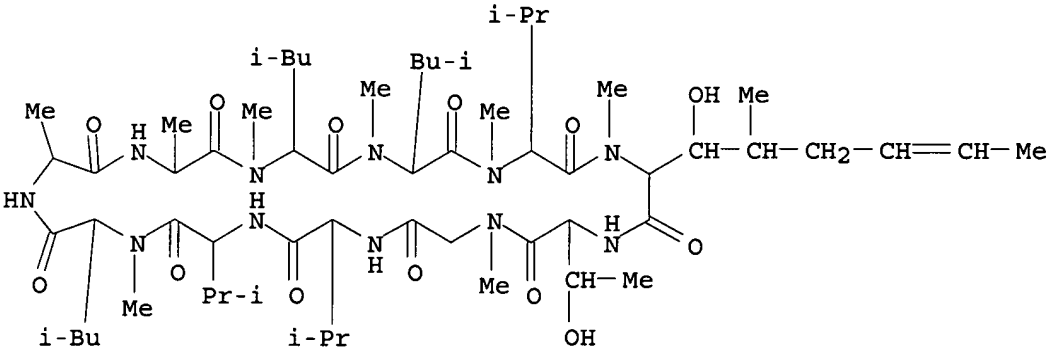

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 15 OF 43 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:178456 HCAPLUS
DOCUMENT NUMBER: 134:223185
TITLE: Biodegradable low molecular weight triblock lactide-glycolide-polyethylene glycol copolymers having reverse thermal gelation properties
INVENTOR(S): Rathi, Ramesh C.; Zentner, Gaylen M.; Jeong, Byeongmoon
PATENT ASSIGNEE(S): Macromed, Inc., USA
SOURCE: U.S., 20 pp., Cont.-in-part of U.S. 6,117,949. CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6201072	B1	20010313	US 1999-396589	19990915
US 6004573	A	19991221	US 1997-943167	19971003
US 6117949	A	20000912	US 1998-164865	19981001
ZA 9809009	A	19990614	ZA 1998-9009	19981002

TR 200000900	T2	20000821	TR 2000-200000900		19981002
PT 1034207	T	20050729	PT 1998-950839		19981002
ES 2239408	T3	20050916	ES 1998-950839		19981002
CA 2345659	AA	20000406	CA 1999-2345659		19990930
WO 2000018821	A1	20000406	WO 1999-US22755		19990930
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RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
BR 9914258	A	20010703	BR 1999-14258		19990930
ZA 200102453	A	20010928	ZA 2001-2453		19990930
EP 1141079	A1	20011010	EP 1999-954698		19990930
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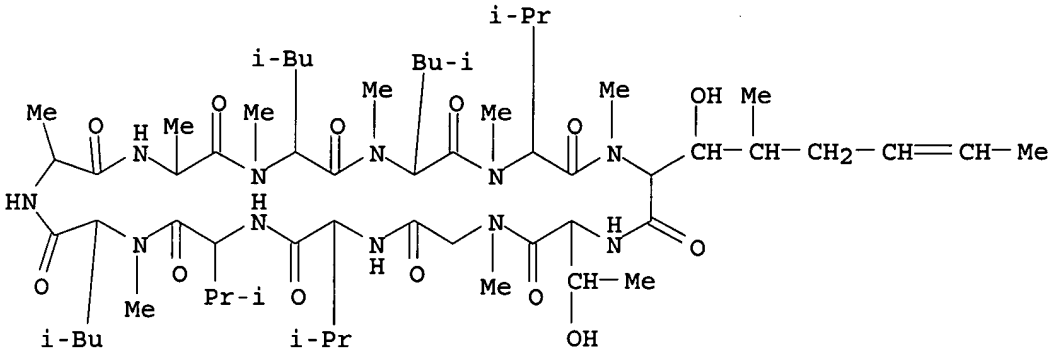
TR 200100900	T2	20011022	TR 2001-200100900		19990930
JP 2002525404	T2	20020813	JP 2000-572276		19990930
NZ 510832	A	20021025	NZ 1999-510832		19990930
AU 758475	B2	20030320	AU 2000-10983		19990930
RU 2232779	C2	20040720	RU 2001-111856		19990930
NO 2001001639	A	20010330	NO 2001-1639		20010330
PRIORITY APPLN. INFO.:			US 1997-943167	A2	19971003
			US 1998-164865	A2	19981001
			US 1999-396589	A	19990915
			WO 1999-US22755	W	19990930

AB A water soluble, biodegradable ABA- or BAB-type tri-block polymer is disclosed that is made up of a major amount of a hydrophobic A polymer block made of a biodegradable polyester and a minor amount of a hydrophilic polyethylene glycol(PEG) B polymer block, having an overall average mol. weight of between about 2000 and 4990, and that possesses reverse thermal gelation properties. Effective concns. of the tri-block polymer and a drug may be uniformly contained in an aqueous phase to form a drug delivery composition At temps. below the gelation temperature of the tri-block polymer the composition is a liquid and at temps. at or above the gelation temperature the composition is a gel or semi-solid. The composition may be administered to a warm-blooded animal as a liquid by parenteral, ocular, topical, inhalation, transdermal, vaginal, transurethral, rectal, nasal, oral, pulmonary or aural delivery means and is a gel at body temperature The composition may also be administered as a gel. The drug is released at a controlled rate from the gel which biodegrades into non-toxic products. The release rate of the drug may be adjusted by changing various parameters such as hydrophobic/hydrophilic component content, polymer concentration, mol. weight and polydispersity of the tri-block polymer. Because the tri-block polymer is amphiphilic, it functions to increase the solubility and/or stability of drugs in the composition

IT **108027-43-6**, Cyclosporins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(biodegradable low-mol.-weight triblock lactide-glycolide-polyethylene glycol copolymers having reverse thermal gelation properties)

RN 108027-43-6 HCAPLUS

CN Cyclosporin S (9CI) (CA INDEX NAME)



REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

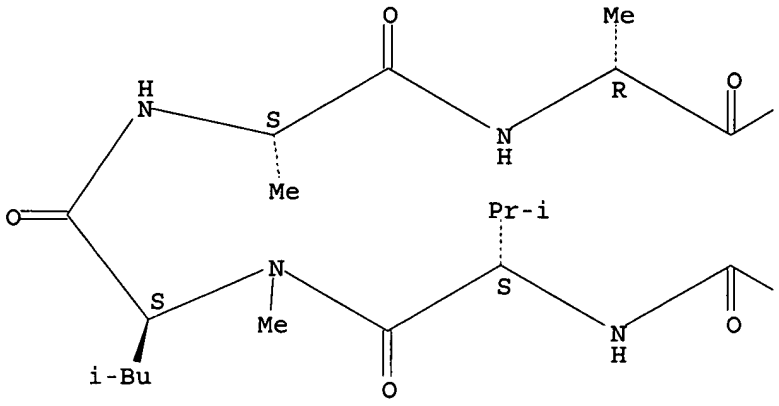
L24 ANSWER 16 OF 43 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:759756 HCAPLUS
DOCUMENT NUMBER: 134:65905
TITLE: Suppression of mitochondrial permeability transition pore and induction of lymphoma P388 cell death by cyclosporin A
AUTHOR(S): Teplova, V.; Evtodienko, Yu.; Odinokova, I.; Kruglov, A.; Kudrjavtsev, A.
CORPORATE SOURCE: Institute of Theoretical and Experimental Biophysics RAS, Pushchino, 142290, Russia
SOURCE: IUBMB Life (2000), 50(1), 75-80
CODEN: IULIF8; ISSN: 1521-6543
PUBLISHER: Taylor & Francis
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Suppression of the mitochondrial permeability transition pore (PTP) and induction of lymphoma P388 cell death were studied in the presence of cyclosporin A (CsA) and its derivs. In expts. with permeabilized P388 cells, CsA and its nonimmunosuppressive derivative N-methyl-Val-4-CsA, but not cyclosporin H (CsH), enhanced Ca2+ accumulation in mitochondria and suppressed PTP opening. Moreover, CsA was able either itself to induce or to enhance a prooxidant-induced P388 programmed cell death. Blebbing and formation of apoptotic bodies were among the observed CsA effects. N-Methyl-Val-4-CsA showed similar effects, but CsH had no effect on P388 cell death. These results show that initial-stage P388 tumor cell death is not related to PTP opening but can be the result of PTP closing with a corresponding increase in the formation of reactive oxygen species.

IT **156047-28-8**, SDZ 220-384
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(suppression of mitochondrial permeability transition pore and induction of lymphoma P388 cell death by cyclosporin A)
RN 156047-28-8 HCAPLUS
CN Cyclosporin A, 9-(N-methyl-L-valine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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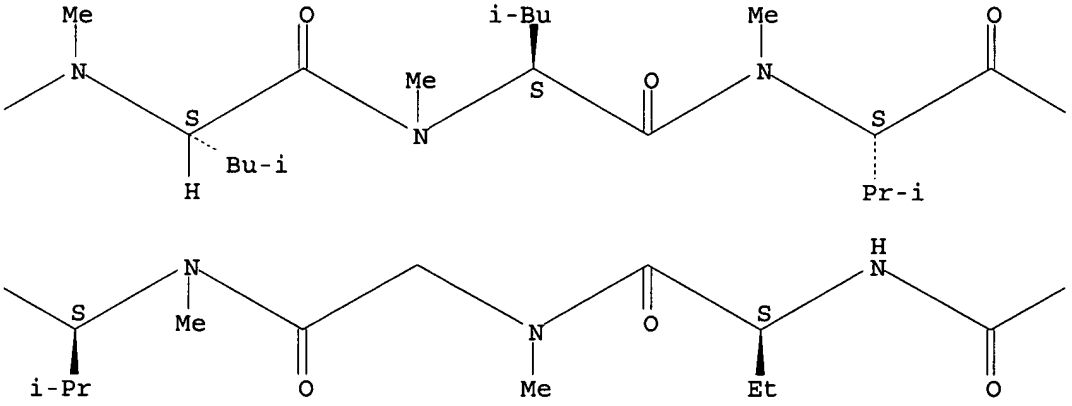

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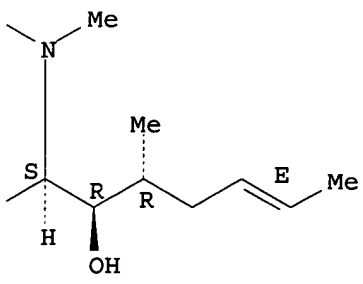


REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 17 OF 43 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:644947 HCAPLUS
DOCUMENT NUMBER: 133:350496
TITLE: Synthetic routes to NEtXaa4-cyclosporin A derivatives as potential anti-HIV I drugs
AUTHOR(S): Hubler, F.; Ruckle, T.; Patiny, L.; Muamba, T.; Guichou, J.-F.; Mutter, M.; Wenger, R.
CORPORATE SOURCE: Institute of Organic Chemistry, University of Lausanne, Lausanne, CH-1015, Switz.
SOURCE: Tetrahedron Letters (2000), 41(37), 7193-7196
CODEN: TELEAY; ISSN: 0040-4039
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 133:350496

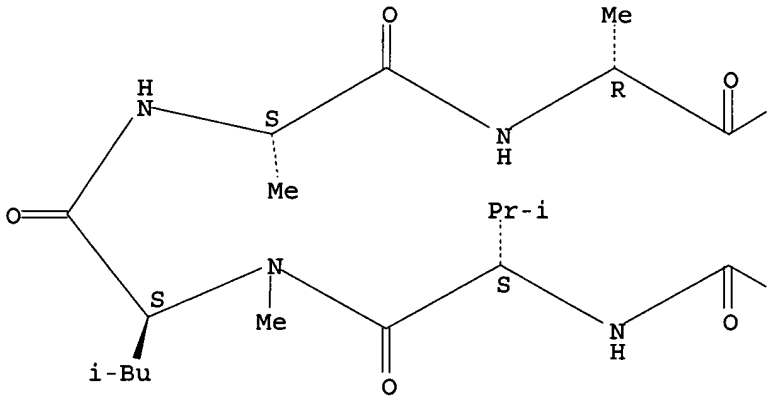
AB An efficient synthesis in 10 steps and overall yields up to 27% of NEtXaa4-cyclosporin A derivs. (NEtXaa = N-ethylated Leu, Val, Ile, Thr) starting from cyclosporin A is described. Biol. activities of the new analogs show promising results for the design of cyclosporin derivs. exhibiting non-immunosuppressive and anti-HIV activity.

IT **254435-90-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of N-Et amino acid-containing cyclosporin A derivs. with non-immunosuppressive and anti-HIV activity)

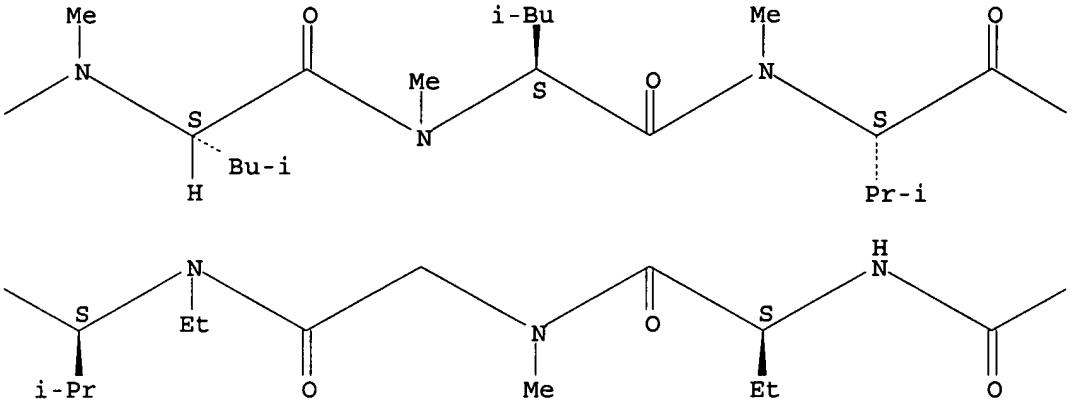
RN 254435-90-0 HCAPLUS
CN Cyclosporin A, 9-(N-ethyl-L-valine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

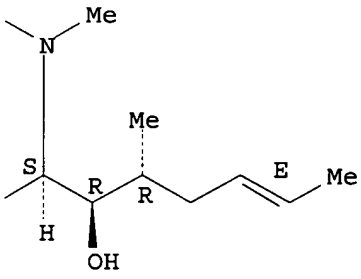
PAGE 1-A



PAGE 1-B



PAGE 1-C



REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 18 OF 43 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:227702 HCAPLUS
DOCUMENT NUMBER: 132:251583
TITLE: Biodegradable low molecular weight triblock polyester-polyethylene glycol copolymers having reverse thermal gelation properties
INVENTOR(S): Rathi, Ramesh C.; Zentner, Gaylen M.; Jeong, Byeongmoon
PATENT ASSIGNEE(S): Macromed, Inc., USA
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000018821	A1	20000406	WO 1999-US22755	19990930

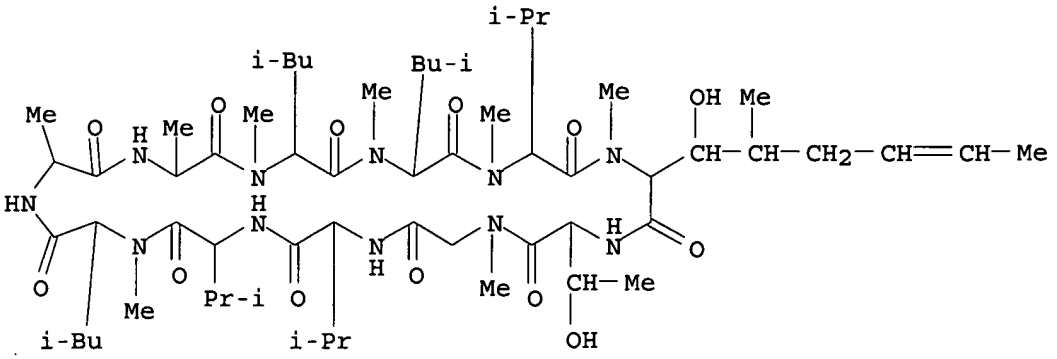
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 6117949	A	20000912	US 1998-164865		19981001
US 6201072	B1	20010313	US 1999-396589		19990915
CA 2345659	AA	20000406	CA 1999-2345659		19990930
BR 9914258	A	20010703	BR 1999-14258		19990930
ZA 200102453	A	20010928	ZA 2001-2453		19990930
EP 1141079	A1	20011010	EP 1999-954698		19990930
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
JP 2002525404	T2	20020813	JP 2000-572276		19990930
NZ 510832	A	20021025	NZ 1999-510832		19990930
AU 758475	B2	20030320	AU 2000-10983		19990930
RU 2232779	C2	20040720	RU 2001-111856		19990930
NO 2001001639	A	20010330	NO 2001-1639		20010330
PRIORITY APPLN. INFO.:			US 1998-164865	A	19981001
			US 1999-396589	A	19990915
			US 1997-943167	A2	19971003
			WO 1999-US22755	W	19990930

AB A water soluble, biodegradable ABA- or BAB-type tri-block polymer is disclosed that is made up of a major amount of a hydrophobic A polymer block made of a biodegradable polyester and a minor amount of a hydrophilic polyethylene glycol(PEG) B polymer block, having an overall average mol. weight of between about 2000 and 4990, and that possesses reverse thermal gelation properties. Effective concns. of the tri-block polymer and a drug may be uniformly contained in an aqueous phase to form a drug delivery composition At temps. below the gelation temperature of the tri-block polymer the composition is a liquid and at temps. at or above the gelation temperature the composition is a gel or semi-solid. The composition may be administered to a warm-blooded animal as a liquid by parenteral, ocular, topical, inhalation, transdermal, vaginal, transurethral, rectal, nasal, oral, pulmonary or aural delivery means and is a gel at body temperature The composition may also be administered as a gel. The drug is released at a controlled rate from the gel which biodegrades into non-toxic products. The release rate of the drug may be adjusted by changing various parameters such as hydrophobic/hydrophilic component content, polymer concentration, mol. weight and polydispersity of the tri-block polymer. Because the tri-block polymer is amphiphilic, it functions to increase the solubility and/or stability of drugs in the composition

IT **108027-43-6**, Cyclosporins
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(biodegradable low-mol.-weight triblock polyester-polyethylene glycol copolymers having reverse thermal gelation properties)

RN 108027-43-6 HCAPLUS
CN Cyclosporin S (9CI) (CA INDEX NAME)



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 19 OF 43 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:34890 HCAPLUS
DOCUMENT NUMBER: 132:88163
TITLE: Novel cyclosporin with improved activity profile, pharmaceutical composition, and use in the treatment of AIDS
INVENTOR(S): Wenger, Roland M.; Mutter, Manfred; Ruckle, Thomas
PATENT ASSIGNEE(S): Debiopharm S.A., Switz.
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000001715	A1	20000113	WO 1999-IB1232	19990630
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2335903	AA	20000113	CA 1999-2335903	19990630
AU 9943856	A1	20000124	AU 1999-43856	19990630
AU 759480	B2	20030417		
BR 9911724	A	20010320	BR 1999-11724	19990630
EP 1091975	A1	20010418	EP 1999-926684	19990630
EP 1091975	B1	20051214		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY				
JP 2002519434	T2	20020702	JP 2000-558116	19990630
US 6927208	B1	20050809	US 2000-720923	19990630
AT 312843	E	20051215	AT 1999-926684	19990630

PRIORITY APPLN. INFO.: CH 1998-1405 A 19980701
WO 1999-IB1232 W 19990630

OTHER SOURCE(S): MARPAT 132:88163
AB The invention concerns a novel cyclosporin, its pharmaceutical use and a

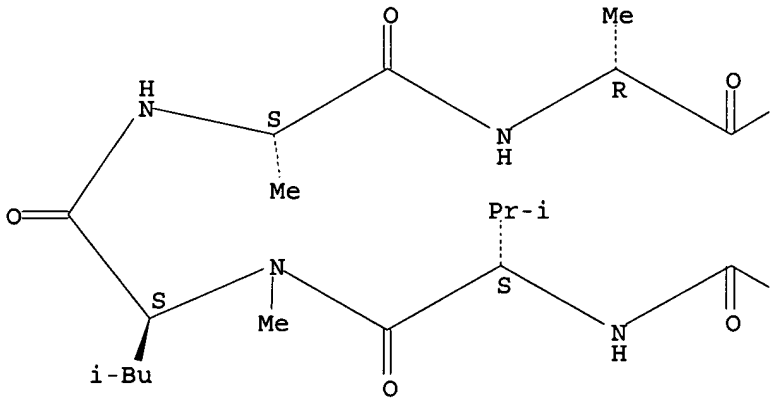
pharmaceutical composition containing it. The cyclosporin derivs. of the invention
inhibit HIV-, while not having the immunosuppressant activity of cyclosporin A,.

IT **254435-90-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(cyclosporin with improved activity profile, pharmaceutical composition, and use in the treatment of AIDS)

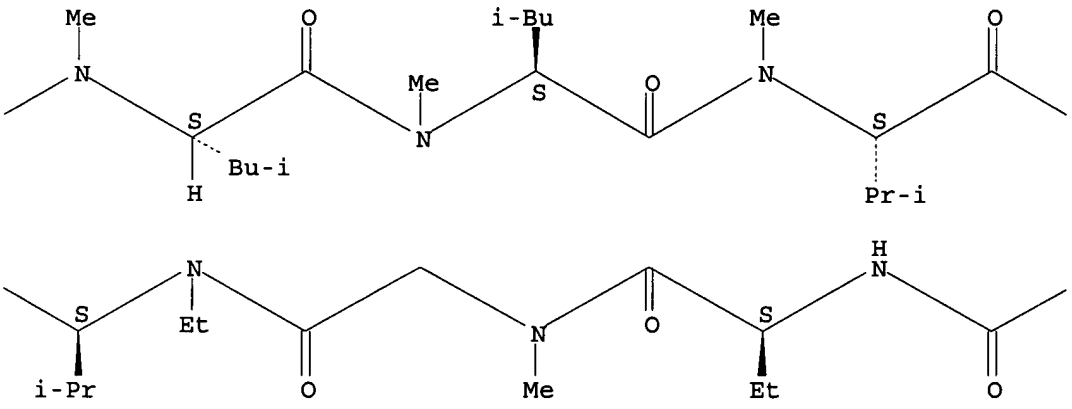
RN 254435-90-0 HCAPLUS
CN Cyclosporin A, 9-(N-ethyl-L-valine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

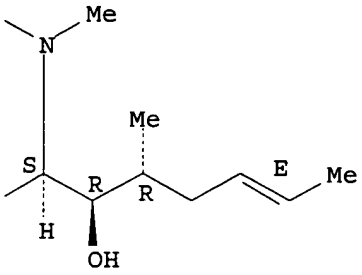
PAGE 1-A



PAGE 1-B



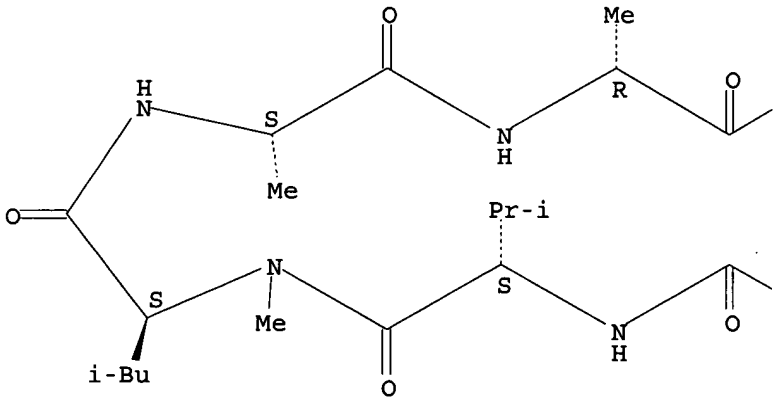
PAGE 1-C



IT **156047-28-8**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cyclosporin with improved activity profile, pharmaceutical composition, and use in the treatment of AIDS)
RN 156047-28-8 HCAPLUS
CN Cyclosporin A, 9-(N-methyl-L-valine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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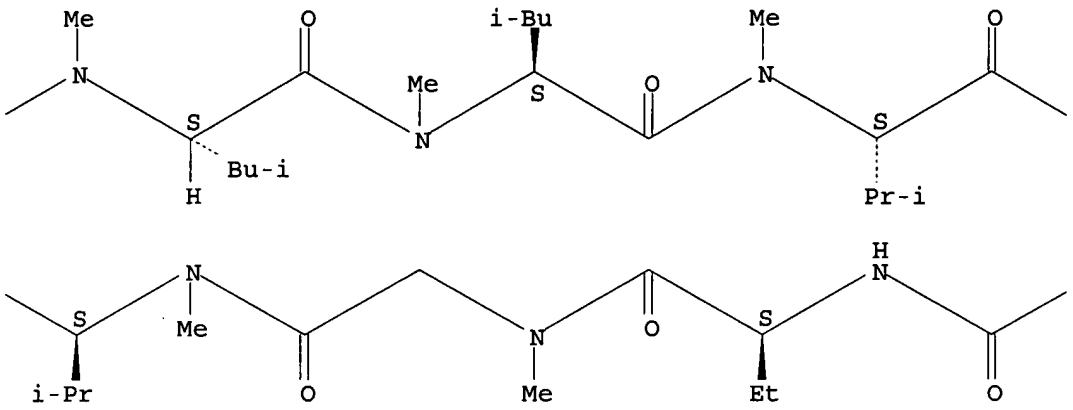

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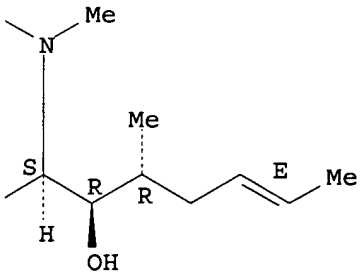


REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 20 OF 43 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:783952 HCAPLUS
DOCUMENT NUMBER: 132:18781
TITLE: Use of cyclosporins in the treatment of inflammatory autoimmune diseases
INVENTOR(S): Hiestand, Peter
PATENT ASSIGNEE(S): Novartis A. -G., Switz.; Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.
SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9962540	A1	19991209	WO 1999-EP3770	19990531

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ,

DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

CA 2333315	AA	19991209	CA 1999-2333315	19990531
AU 9943724	A1	19991220	AU 1999-43724	19990531
AU 750422	B2	20020718		
BR 9910860	A	20010306	BR 1999-10860	19990531
EP 1082130	A1	20010314	EP 1999-926489	19990531
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, FI				
JP 2002516873	T2	20020611	JP 2000-551796	19990531
ZA 2000006464	A	20020311	ZA 2000-6464	20001109
NO 2000006113	A	20010125	NO 2000-6113	20001201
PRIORITY APPLN. INFO.:			GB 1998-11854 A	19980602
			WO 1999-EP3770 W	19990531

OTHER SOURCE(S): MARPAT 132:18781

AB Non-immunosuppressive, cyclophilin-binding cyclosporins are useful in the treatment and prevention of inflammatory autoimmune diseases, such as rheumatoid arthritis. E.g., [MeIle]4-ciclosporin showed good inhibition of swelling of hind paw in the rat collagen-induced arthritis model at oral doses of 12.5 and 25 mg/kg twice daily up to approx. 60% of the effect of the proprietary COX inhibitor (used as control) at day 9 (dosed at 2.5 mg/kg twice daily, orally).

IT **156047-28-8**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

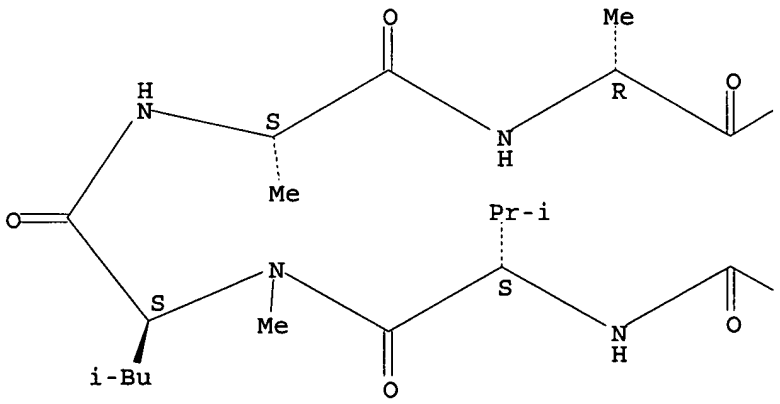
(non-immunosuppressive cyclophilin-binding cyclosporins for treatment of inflammatory autoimmune diseases)

RN 156047-28-8 HCAPLUS

CN Cyclosporin A, 9-(N-methyl-L-valine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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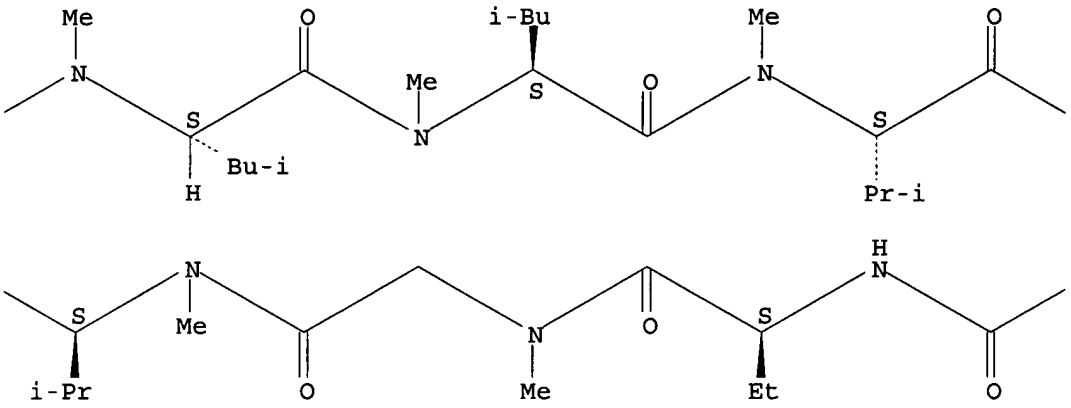

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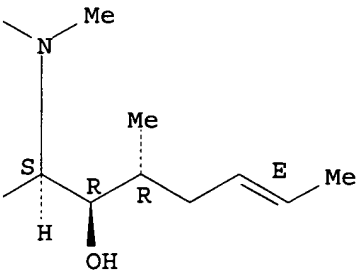


REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 21 OF 43 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:265889 HCAPLUS
DOCUMENT NUMBER: 130:306591
TITLE: Method using pentosan polysulfate for preventing nephrotoxicity caused by cyclosporins and tacrolimus
INVENTOR(S): Striker, Gary E.; Striker, Lilliane; Kortright, Kenneth H.
PATENT ASSIGNEE(S): Baker Norton Pharmaceuticals, Inc., USA; United States Dept. of Health and Human Services
SOURCE: PCT Int. Appl., 32 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9918961	A1	19990422	WO 1998-US21313	19981009

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

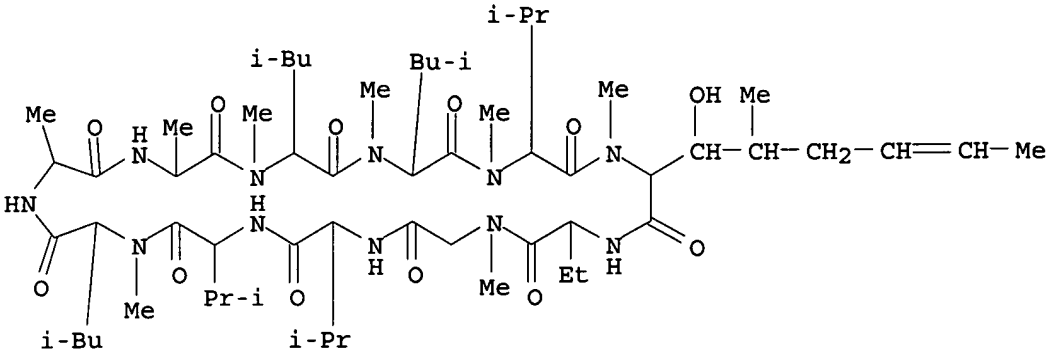
US 6187745	B1	20010213	US 1998-168974		19981001
CA 2304374	AA	19990422	CA 1998-2304374		19981009
AU 9897943	A1	19990503	AU 1998-97943		19981009
AU 748495	B2	20020606			
EP 1027053	A1	20000816	EP 1998-952186		19981009
EP 1027053	B1	20040616			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
BR 9813860	A	20010320	BR 1998-13860		19981009
JP 2001519392	T2	20011023	JP 2000-515596		19981009
NZ 503493	A	20011130	NZ 1998-503493		19981009
RU 2191020	C2	20021020	RU 2000-111495		19981009
AT 269098	E	20040715	AT 1998-952186		19981009
PT 1027053	T	20040930	PT 1998-952186		19981009
ES 2221714	T3	20050101	ES 1998-952186		19981009
NO 2000001828	A	20000515	NO 2000-1828		20000407
HK 1026845	A1	20041210	HK 2000-105823		20000915
PRIORITY APPLN. INFO.:			US 1997-62947P	P	19971009
			US 1998-168974	A	19981001
			WO 1998-US21313	W	19981009

AB A method is provided for preventing, reducing, or reversing nephrotoxicity or renal dysfunction induced by administration of a cyclosporin or tacrolimus to a mammalian patient. The method comprises the co-administration to the patient, either before, together with or after cyclosporin or tacrolimus administration, of a pharmaceutical composition containing an effective amount of pentosan polysulfate (PPS) or a pharmaceutically acceptable salt thereof. The oral route of administration is preferred. The total daily dosage of PPS or PPS salt ranges from about 2 to about 50 mg/kg of patient body weight, or about 140 to about 3500 mg per day in adult human patients. Also disclosed are a method of providing immunosuppressive therapy to a patient while avoiding cyclosporin or tacrolimus-induced nephrotoxicity, and combination pharmaceutical compns. to be used in such therapy.

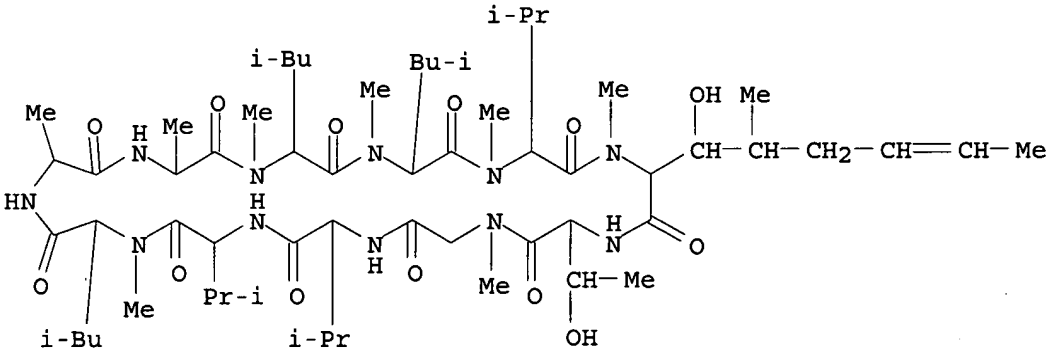
IT **108027-42-5**, Cyclosporin Q **108027-43-6**, Cyclosporin S
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pentosan polysulfate for preventing nephrotoxicity caused by cyclosporins and tacrolimus)

RN 108027-42-5 HCAPLUS

CN Cyclosporin Q (9CI) (CA INDEX NAME)



RN 108027-43-6 HCAPLUS
CN Cyclosporin S (9CI) (CA INDEX NAME)



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 22 OF 43 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:799989 HCAPLUS
DOCUMENT NUMBER: 130:43304
TITLE: Method and compositions for administering taxanes orally to human patients using a cyclosporin to enhance bioavailability
INVENTOR(S): Broder, Samuel; Duchin, Kenneth L.; Selim, Sami
PATENT ASSIGNEE(S): Baker Norton Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9853811	A1	19981203	WO 1998-US7776	19980422

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT,

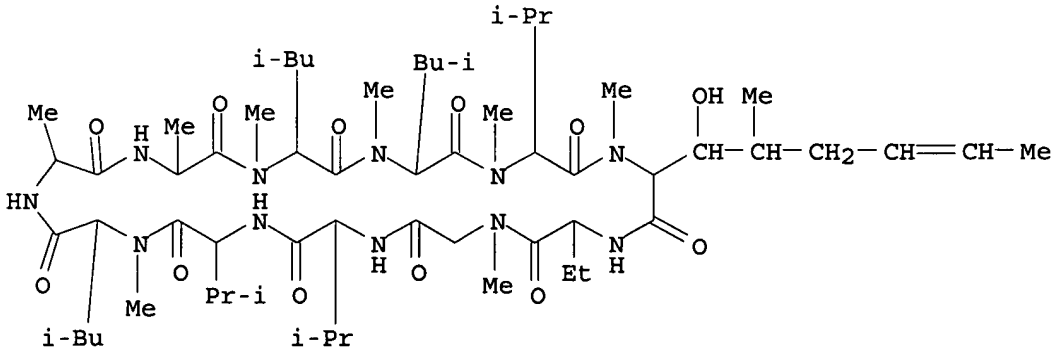
	UA, UG, UZ, VN, YU, ZW				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA	2290446	AA	19981203	CA 1998-2290446	19980422
AU	9871300	A1	19981230	AU 1998-71300	19980422
EP	994706	A1	20000426	EP 1998-918361	19980422
EP	994706	B1	20051102		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, RO				
BR	9809694	A	20001003	BR 1998-9694	19980422
JP	2002500667	T2	20020108	JP 1999-500663	19980422
RU	2205005	C2	20030527	RU 1999-128033	19980422
NZ	516026	A	20030630	NZ 1998-516026	19980422
CN	1550231	A	20041201	CN 2004-10030478	19980422
AT	308365	E	20051115	AT 1998-918361	19980422
ZA	9804268	A	19990623	ZA 1998-4268	19980520
HK	1026637	A1	20060106	HK 2000-105943	20000920
PRIORITY APPLN. INFO.:				US 1997-863513 A	19970527
				NZ 1998-501127 A1	19980422
				WO 1998-US7776 W	19980422

AB Taxane antineoplastic agents which have heretofore exhibited poor or non-existent oral bioavailability are administered orally to human patients suffering from taxane-responsive disease conditions and made sufficiently bioavailable to achieve therapeutic blood levels. In a preferred embodiment, the taxane, preferably paclitaxel, is co-administered to the patient with an oral cyclosporin enhancing agent, preferably cyclosporin A. By one preferred method, a dose of oral enhancer is administered about 0.5-72 h before the taxane and a second dose of the enhancer and administered immediately before, together with or immediately after the taxane. A method of treating human patients suffering from taxane-responsive disease conditions is also provided, as well as a method for providing such treatment while preventing or reducing hypersensitivity and allergic reactions without the need for pre-medication.

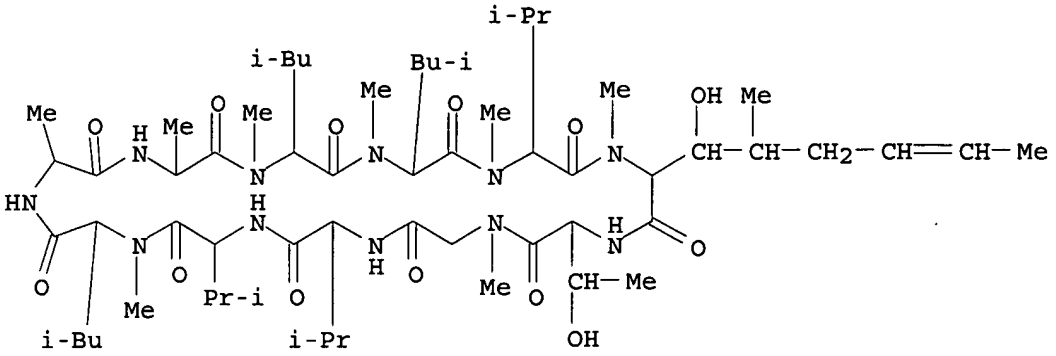
IT **108027-42-5**, Cyclosporin Q **108027-43-6**, Cyclosporin S
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method and compns. for administering taxanes orally to human patients using a cyclosporin to enhance bioavailability)

RN 108027-42-5 HCAPLUS

CN Cyclosporin Q (9CI) (CA INDEX NAME)



RN 108027-43-6 HCAPLUS
CN Cyclosporin S (9CI) (CA INDEX NAME)



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 23 OF 43 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:576450 HCAPLUS
DOCUMENT NUMBER: 129:285749
TITLE: Biphasic effects of cyclosporin A on formyl-methionyl-leucyl-phenylalanine stimulated responses in HL-60 cells differentiated into neutrophils
AUTHOR(S): Nguyen, Nathalie S. D.; Pulido, Silvia M.; Ruegg, Urs T.
CORPORATE SOURCE: Pharmacology Group, School of Pharmacy, University of Lausanne, Lausanne, 1015, Switz.
SOURCE: British Journal of Pharmacology (1998), 124(8), 1774-1780
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Stockton Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The immunosuppressive drug cyclosporin A (CsA) depresses neutrophil oxidative burst which may lead to an increased susceptibility to infection in transplant patients. Using specific CsA analogs we investigated the mechanism of inhibition of the oxidative burst and evaluated short and long-term effects of CsA on dimethylsulfoxide-differentiated HL-60 neutrophils. A biphasic pattern was observed: a 4 h pre-treatment with CsA (1 μM) diminished the fMLP induced [Ca2+]c rise, reactive oxygen species (ROS) production, and β-glucuronidase release by about 40%, whereas a 20 h pre-treatment increased these responses by about 1.5 fold. [MeVal4]CsA, which binds with high affinity to cyclophilin but inhibits the interaction of the CsA-cyclophilin complex with calcineurin, blocked the stimulation observed with CsA after a 20 h incubation but did not alter the CsA effects after a 4 h pre-treatment. PSC 833 (1 μM), a potent multi-drug resistance transporter (MDR) inhibitor, diminished ROS production to the same extent as a 4 h CsA incubation but was ineffective after a 20 h pre-treatment. An involvement of MDR as a basis for CsA or PSC 833 action was ruled out based on the results of the calcein retention assay. [3H]CsA uptake showed that CsA and [MeVal4]CsA, but not CsH or PSC 833 were strongly taken up and retained by the cells. In conclusion, the reduction of the responses after 4 h appear to be due to a primary reduction of calcium signaling, while the enhanced responses after 20 h may be due to

calcineurin inhibition.

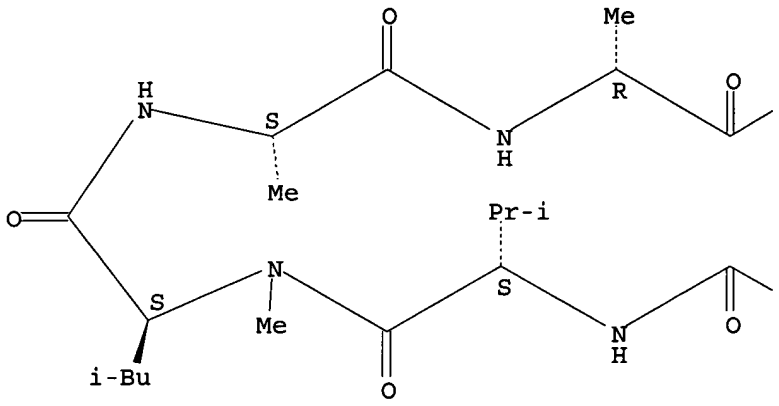
IT **156047-28-8**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(biphasic effects of cyclosporin A on fMLP-stimulated responses in HL-60 cells differentiated into neutrophils)

RN 156047-28-8 HCAPLUS

CN Cyclosporin A, 9-(N-methyl-L-valine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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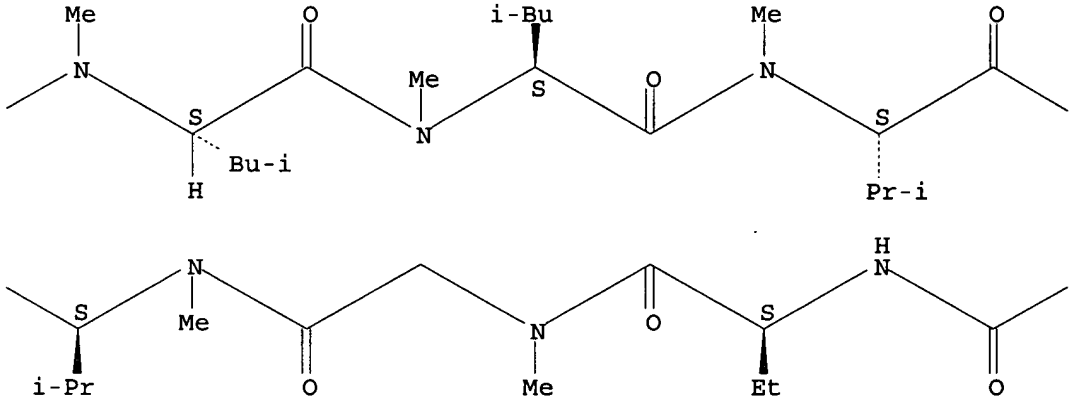
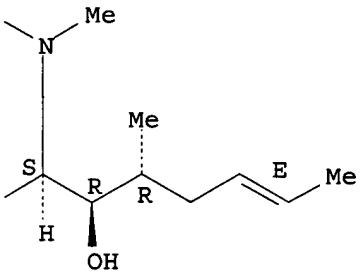




REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 24 OF 43 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:571324 HCAPLUS
DOCUMENT NUMBER: 129:339480
TITLE: Cyclosporins: lack of correlation between antischistosomal properties and inhibition of cyclophilin isomerase activity
AUTHOR(S): Khattab, A.; Pica-Mattoccia, L.; Klinkert, M. Q.; Wenger, R.; Cioli, D.
CORPORATE SOURCE: Consiglio Nazionale delle Ricerche, Istituto di Biologia Cellulare, Rome, Italy
SOURCE: Experimental Parasitology (1998), 90(1), 103-109
CODEN: EXPAAA; ISSN: 0014-4894
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

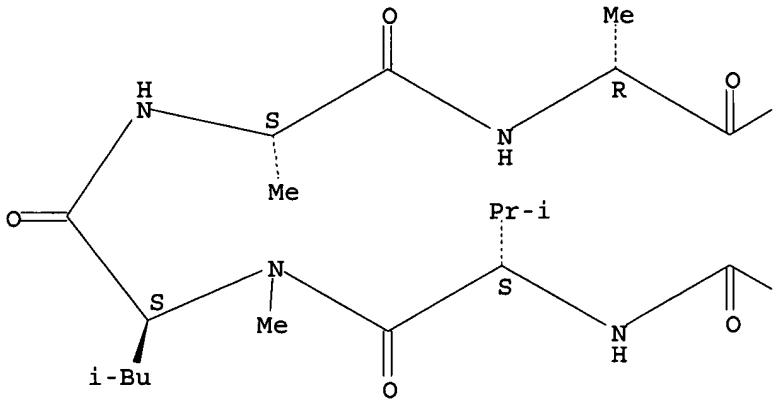
AB The immunosuppressive fungal products cyclosporin A (CsA) and FK506 bind with high affinity to intracellular receptor proteins: cyclophilin (CYP) is one of the receptors for CsA and FK506-binding protein (FKBP) is one of the receptors for FK506. These proteins catalyze the in vitro isomerization from a cis to a trans conformation of peptidyl-prolyl bonds in oligopeptides. The relative importance of the peptidyl-prolyl cis-trans isomerase (PPIase) activity of CYP compared to FKBP in schistosomes is not known. Here, we examine the effects of CsA and FK506 and show that the former inhibits PPIase activity in schistosome exts., whereas the latter does not. Since CsA is specific for the CYP protein, this result is indicative of the fact that the PPIase activity in the parasite is mostly attributable to CYP. The observation that CsA was significantly more effective than FK506 as an antischistosomal agent, both in vivo and in vitro raises the possibility that killing of schistosomes is caused by the inhibition of schistosome CYP PPIase. We compared a number of Cs analogs for their antischistosomal effects and for the inhibition of CYP PPIase, but were unable to find a correlation between the two properties. We therefore conclude that the lethal effect of CsA is not directly linked to the inhibition of the enzymic activity of schistosome CYPs. (c) 1998 Academic Press.

IT **156047-28-8**, SDZ 220-384
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lack of correlation between antischistosomal properties of

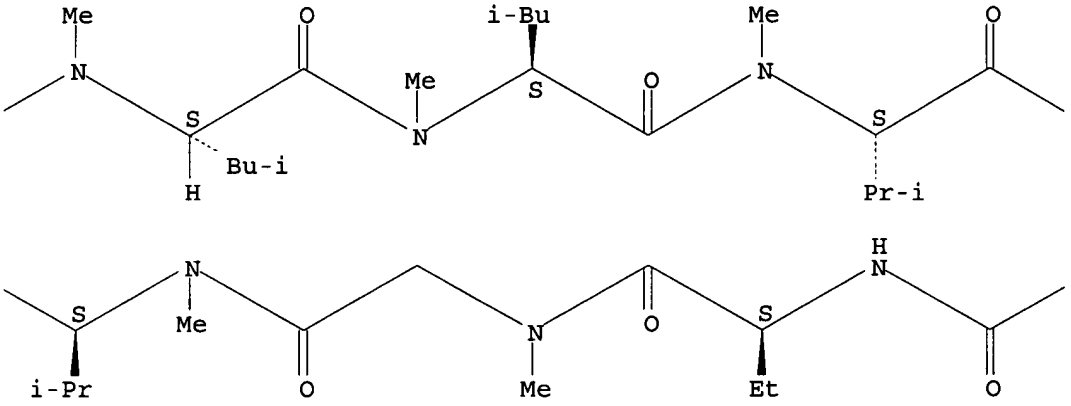
cyclosporins and inhibition of cyclophilin isomerase activity)
RN 156047-28-8 HCAPLUS
CN Cyclosporin A, 9-(N-methyl-L-valine)- (9CI) (CA INDEX NAME)

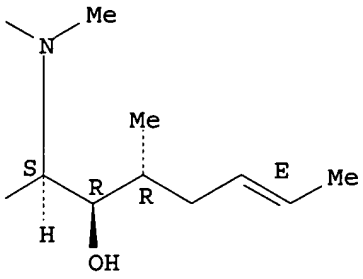
Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B





REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 25 OF 43 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:450141 HCAPLUS
DOCUMENT NUMBER: 127:76017
TITLE: nonimmunosuppresive cyclosporins as cyclophilin rotamase inhibitors for treatment of neurodegenerative diseases
INVENTOR(S): Steiner, Joseph P.; Hamilton, Gregory S.; Snyder, Solomon H.
PATENT ASSIGNEE(S): Guilford Pharmaceuticals Inc., USA; Johns Hopkins University School of Medicine
SOURCE: PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9718828	A1	19970529	WO 1996-US17677	19961115
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
JP 09143198	A2	19970603	JP 1996-111414	19960502
JP 3089350	B2	20000918		
CA 2238050	AA	19970529	CA 1996-2238050	19961115
AU 9677210	A1	19970611	AU 1996-77210	19961115
AU 714482	B2	20000106		
EP 880358	A1	19981202	EP 1996-940289	19961115
EP 880358	B1	20030806		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
CN 1207043	A	19990203	CN 1996-199455	19961115
CN 1123360	B	20031008		
BR 9611624	A	19990601	BR 1996-11624	19961115

AT 246510	E	20030815	AT 1996-940289	19961115
ES 2206608	T3	20040516	ES 1996-940289	19961115
NO 9802264	A	19980720	NO 1998-2264	19980518
LV 12125	B	19981220	LV 1998-114	19980716
US 6444643	B1	20020903	US 1999-321762	19990528
US 2003013645	A1	20030116	US 2002-199107	20020722
PRIORITY APPLN. INFO.:			US 1995-560685	A 19951120
			WO 1996-US17677	W 19961115
			US 1999-321762	A1 19990528

OTHER SOURCE(S): MARPAT 127:76017

AB A method is disclosed of using neurotrophic cyclophilin inhibitor compds. having an affinity for cyclophilin-type immunophilins as inhibitors of peptidyl-prolyl isomerase (rotamase) enzyme activity. The compds. of the invention, nonimmunosuppresive cyclosporins, may be used for treatment of neurol. disorders coused by brain or spinal cord injuries and neurodegenerative disorders, e.g. Alzheimer's disease, Parkinson's disease, or other neuropathies.

IT **156047-28-8**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

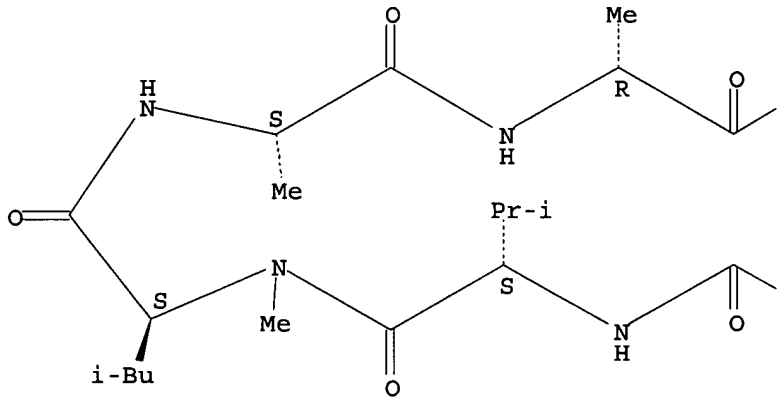
(nonimmunosuppresive cyclosporins as cyclophilin rotamase inhibitors and neurotrophic factors for treatment of neuropathies)

RN 156047-28-8 HCAPLUS

CN Cyclosporin A, 9-(N-methyl-L-valine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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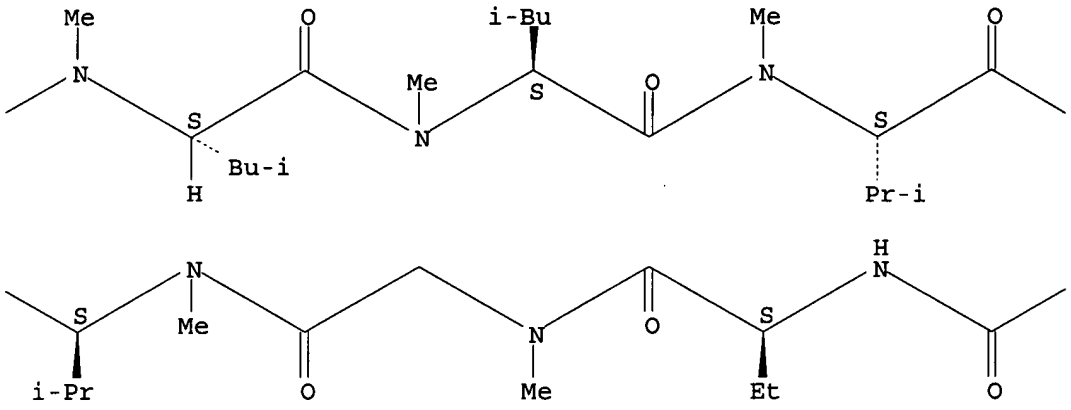
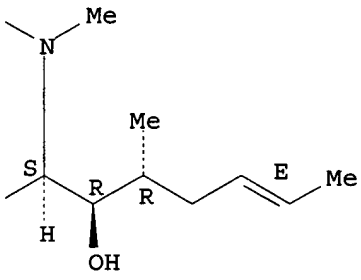


PAGE 1-C



L24 ANSWER 26 OF 43 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:434928 HCAPLUS
DOCUMENT NUMBER: 127:174349
TITLE: Nitric oxide induces apoptosis via triggering mitochondrial permeability transition
AUTHOR(S): Hortelano, Sonsoles; Dallaporta, Bruno; Zamzami, Naoufal; Hirsch, Tamara; Susin, Santos A.; Marzo, Isabel; Bosca, Lisardo; Kroemer, Guido
CORPORATE SOURCE: CNRS-UPR420, 19 Rue Guy Moquet, B.P. 8, Villejuif, F-94801, Fr.
SOURCE: FEBS Letters (1997), 410(2,3), 373-377
CODEN: FEBLAL; ISSN: 0014-5793
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Nitric oxide induces apoptosis in thymocytes, peripheral T cells, myeloid cells and neurons. Here we show that NO is highly efficient in inducing mitochondrial permeability transition, thereby causing the liberation of apoptogenic factors from mitochondria which can induce nuclear apoptosis (DNA condensation and DNA fragmentation) in isolated nuclei in vitro. In intact thymocytes, NO triggers disruption of the mitochondrial

transmembrane potential, followed by hypergeneration of reactive oxygen species, exposure of phosphatidyl serine on the outer plasma membrane leaflet, and nuclear apoptosis. Inhibitors of mitochondrial permeability transition such as bongkrekic acid and a cyclophilin D-binding cyclosporin A derivative, N-methyl-Val-4-cyclosporin A, prevent the mitochondrial as well as all post-mitochondrial signs of apoptosis induced by NO including nuclear DNA fragmentation and exposure of phosphatidylserine residues on the cell surface. These findings indicate that NO can cause apoptosis via triggering of permeability transition.

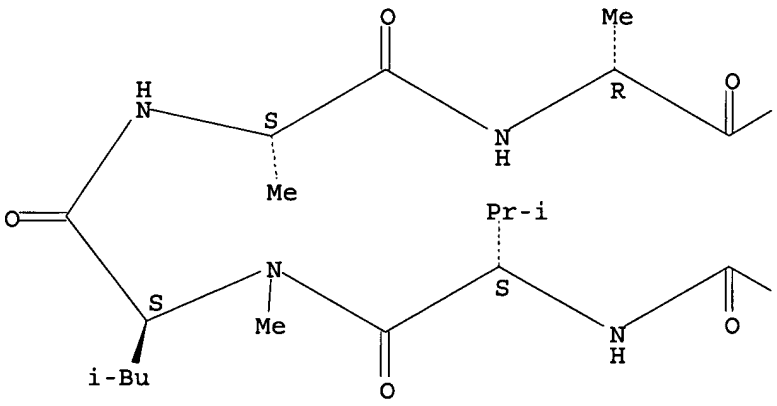
IT **156047-28-8**, SDZ 220-384
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors of mitochondrial permeability transition such as bongkrekic acid, cyclosporin A and SDZ 220-384 prevent apoptosis induced by NO)

RN 156047-28-8 HCAPLUS

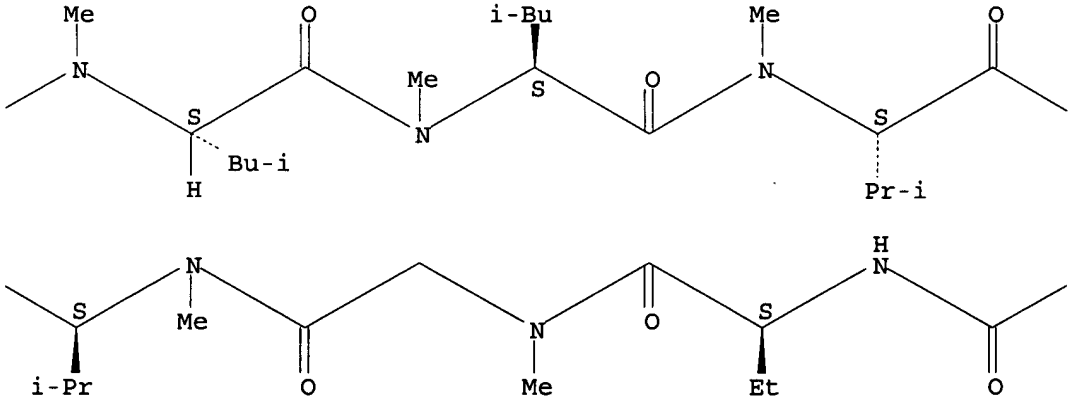
CN Cyclosporin A, 9-(N-methyl-L-valine)- (9CI) (CA INDEX NAME)

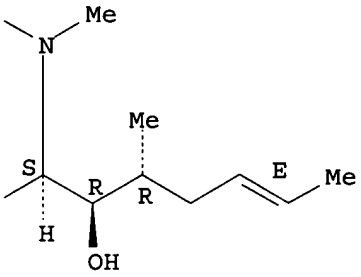
Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B





REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

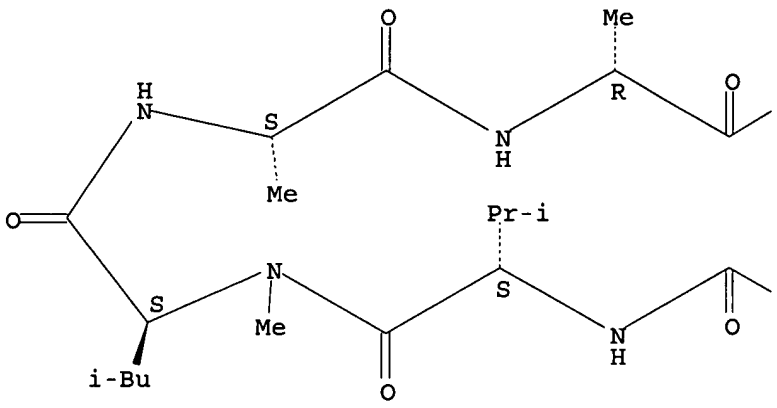
L24 ANSWER 27 OF 43 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:366197 HCAPLUS
DOCUMENT NUMBER: 127:95603
TITLE: Solid-phase total synthesis of cyclosporin analogs
AUTHOR(S): Ko, Soo Y.; Wenger, Roland M.
CORPORATE SOURCE: Sandoz Pharma Ltd., Basel, CH-4002, Switz.
SOURCE: Helvetica Chimica Acta (1997), 80(3), 695-705
CODEN: HCACAV; ISSN: 0018-019X
PUBLISHER: Verlag Helvetica Chimica Acta
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Syntheses of cyclosporin analogs are reported wherein the peptide couplings were achieved in solid phase. The Wang resin was used as the solid support, and the peptide couplings commenced with the residue 11 of the cyclosporin skeleton. The couplings proceeded in a stepwise manner up to the residue MeBmt1, using sym. anhydrides. The peptides were then cleaved of the resin, and the cyclization was achieved in solution using Castros' reagent. The solid-phase synthesis described herein offers a very efficient method for the rapid synthesis of structurally diverse cyclosporin analogs in small quantities. The biol. activities of the synthetic cyclosporin analogs were evaluated in 2 in-vitro assays, including the IL-2 reporter gene assay and the cyclophilin binding assay. The structure-activity relationship is discussed.

IT **156047-28-8P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(solid-phase total synthesis of cyclosporin analogs as immunosuppressants)
RN 156047-28-8 HCAPLUS
CN Cyclosporin A, 9-(N-methyl-L-valine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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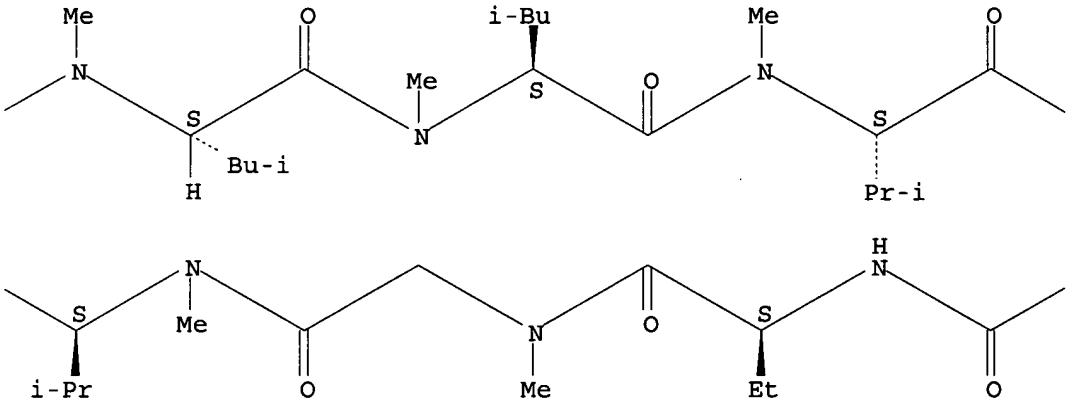

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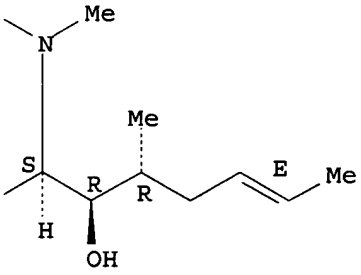


L24 ANSWER 28 OF 43 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:92683 HCAPLUS
DOCUMENT NUMBER: 126:194988
TITLE: Cyclosporin A and its non-immunosuppressive derivative exhibit a differential effect on cell-mediated mineralization in culture
AUTHOR(S): Klein, B.Y.; Gal, I.; Mosheiff, R.; Liebergall, M.; Ben-Bassat, H.
CORPORATE SOURCE: Laboratory of Experimental Surgery Hadassah Medical Center, Ein-Kerem Jerusalem, Israel
SOURCE: Journal of Cellular Biochemistry (1997), 64(2), 209-216
CODEN: JCEBD5; ISSN: 0730-2312
PUBLISHER: Wiley-Liss
DOCUMENT TYPE: Journal
LANGUAGE: English

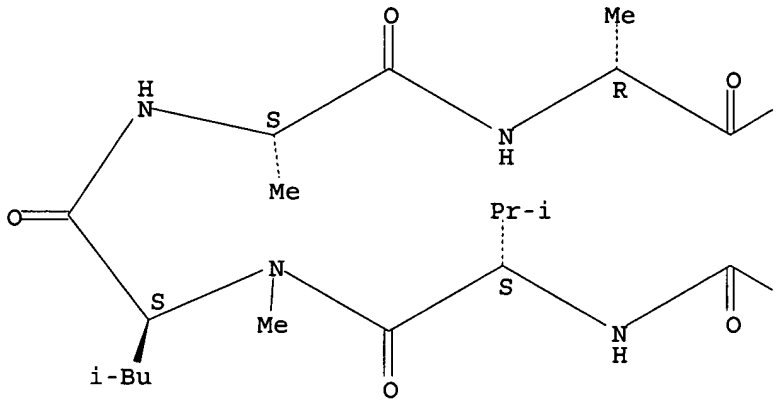
AB Chronic immunosuppressive treatment with cyclosporin A (CsA) is associated with decreased bone d. However, in culture, CsA inhibits osteoclast differentiation and bone resorption. This raises the question as to whether CsA also affects osteoblast function. Immunophilin, one of the CsA-binding cyclophilins that is implicated in the immunosuppressive action of CsA via calcineurin, is a peptidyl prolyl cis-trans isomerase (PPI). CsA also binds a mitochondrial membrane PPI which is implicated in controlling permeability transition pores. Therefore, in the present study the authors tested the effect of CsA on cell mediated mineralization in parallel with mitochondrial rhodamine retention as an indicator of mitochondrial membrane potential. Rat marrow stromal cells were grown in dexamethasone (DEX) medium to stimulate mineralization in culture, and CsA was added to various cultures using different treatment schedules. Low dose (0.1 μM) CsA inhibited mineralization, compared to controls, when present in the cultures during days 3-11 of DEX stimulation. Contrarily, high dose CsA (1.0 μM) resisted the inhibitory effect of the low dose. SDZ 220-384 (SDZ), a non-immunosuppressive derivative of CsA which is known, like CsA, to bind to mitochondrial cyclophilin but does not inhibit calcineurin, was also tested. Both high and low doses of SDZ decreased mineralization when present in the cultures from day 3 or from day 0. The similar effect of the low CsA dose and SDZ on mineralization is in accord with their ability to block permeability transition pores. The differential effect, on day 21 mineralization, between high CsA dose and SDZ took place in parallel to their opposing effects on mitochondrial membrane potential. On days 4-8, mitochondrial rhodamine retention was higher under CsA than under SDZ. Under these conditions there was no significant difference between the effects of these drugs on cell proliferation measured on day 11; there was a minor decrease in specific alkaline phosphatase activity by SDZ, too small to explain the extent of mineralization inhibition by SDZ. These results suggest that permeability transition pores might be involved in controlling mineralization. Unlike SDZ, CsA exhibits an addnl. effect on the mitochondrial membrane potential and on mineralization when applied at a high dose on day 3. Therefore identifying the addnl. activity of high dose CsA, which is missing in SDZ, may be beneficial. Such activity is expected to resist changes in rhodamine retention and decreased mineralization induced by SDZ, and yet enable preservation of immunosuppressive activity of CsA.

IT **156047-28-8**, SDZ 220-384
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(cyclosporin A and non-immunosuppressive derivative exhibit a differential effect on bone marrow stromal cell-mediated mineralization in culture in relation to mitochondrial membrane potential and alkaline phosphatase)
RN 156047-28-8 HCAPLUS

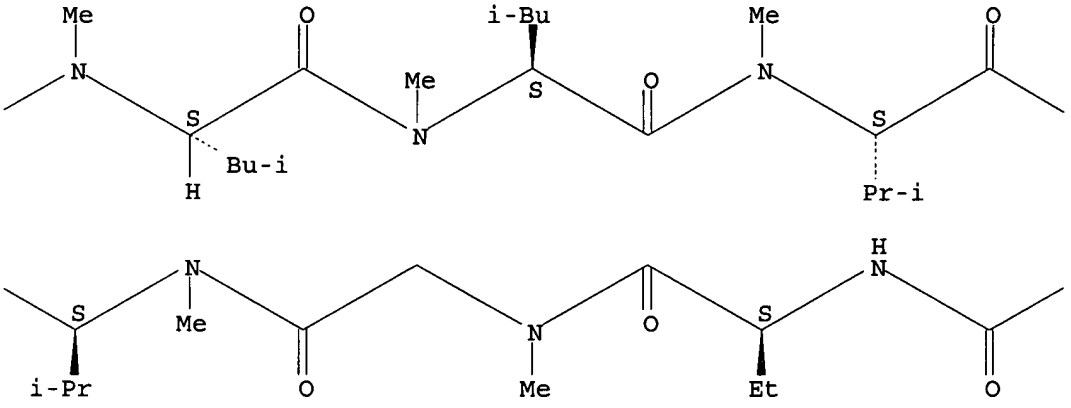
CN Cyclosporin A, 9-(N-methyl-L-valine)- (9CI) (CA INDEX NAME)

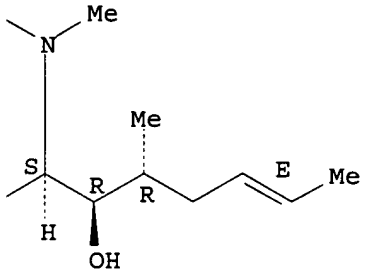
Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B

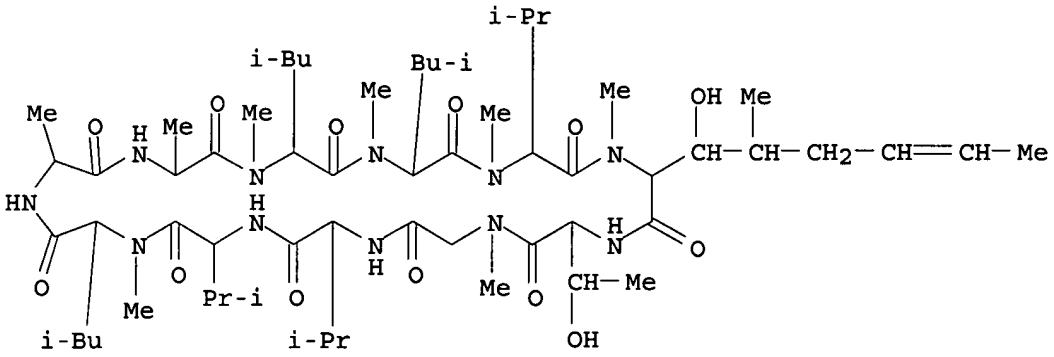




L24 ANSWER 29 OF 43 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:972232 HCAPLUS
DOCUMENT NUMBER: 124:75277
TITLE: Regulation of human mast cell and basophil function
AUTHOR(S): Marone, Gianni; Spadaro, Giuseppe; Genovese, Arturo
CORPORATE SOURCE: School Medicine, University Naples Federico II, Naples, Italy
SOURCE: Progress in Allergy and Clinical Immunology, Proceedings of the International Congress of Allergology and Clinical Immunology, 15th, Stockholm, June 26-July 1, 1994 (1995), Meeting Date 1994, 19-25. Editor(s): Johansson, Stig G. O. Hogrefe & Huber: Seattle, Wash.
CODEN: 62BPA4
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English

AB A review, with 64 refs. Human basophils and mast cells play a fundamental role in the pathogenesis of allergic disorders through the elaboration of proinflammatory mediators and immunoregulatory cytokines. Altered basophil/mast cell releasability has been documented in patients with allergic disorders (bronchial asthma, allergic rhinitis, atopic dermatitis, and chronic urticaria). Basophil and mast cell releasability can be modulated in vitro by nimesulide, a recently identified nonsteroidal anti-inflammatory drug, corticosteroids, type IV cAMP phosphodiesterase inhibitors, protein kinase inhibitors, and immunophillin ligands (cyclosporins and FK-506). The latter group of agents are of particular interest since they exert immunosuppressive and anti-inflammatory effects on human basophils and mast cells in vitro as well in vivo.

IT **108027-43-6**, Cyclosporins
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(regulation of human mast cell and basophil function in relation to inflammatory disease treatment)
RN 108027-43-6 HCAPLUS
CN Cyclosporin S (9CI) (CA INDEX NAME)



L24 ANSWER 30 OF 43 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:598145 HCAPLUS
DOCUMENT NUMBER: 123:132347
TITLE: Cyclosporin A potentiates the dexamethasone-induced mouse mammary tumor virus-chloramphenicol acetyltransferase activity in LMCAT cells: a possible role for different heat shock protein-binding immunophilins in glucocorticosteroid receptor-mediated gene expression
AUTHOR(S): Renoir, Jack-Michel; Mercier-Bodard, Christine; Hoffmann, Kai; Le Bihan, Stephane; Ning, Yang-Min; Sanchez, Edwin R.; Handschumacher, Robert E.; Baulieu, Etienne-Emile
CORPORATE SOURCE: Lab. Hormones, Le Kremlin-Bicetre, 94276, Fr.
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1995), 92(11), 4977-81
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB As previously observed for FK506, the authors report here that cyclosporin A (CsA) treatment of mouse fibroblast cells stably transfected with the mouse mammary tumor virus-chloramphenicol acetyltransferase (MMTV-CAT) reporter plasmid (LMCAT cells) results in potentiation of dexamethasone (Dex)-induced CAT gene expression. Potentiation by CsA is observed in cells treated with 10-100 nM Dex but not in cells treated with 1 μM Dex, a concentration of hormone which results in maximum CAT activity. At 10 nM Dex, 1-5 μM CsA provokes an ≈50-fold increase in CAT gene transcription, compared with transcription induced by Dex alone. No induction of CAT gene expression is observed in cells treated with CsA or FK506 in the absence of Dex. The antisteroid RU 486 abolishes effects obtained in the presence of Dex. Using a series of CsA, as well as FK506, analogs, including some devoid of calcineurin phosphatase inhibition activity, the authors conclude that the potentiation effects of these drugs on Dex-induced CAT gene expression in LMCAT cells do not occur through a calcineurin-mediated pathway. Western-blotting expts. following immunopptn. of glucocorticosteroid receptor (GR) complexes resulted in copptn. of GR, heat shock protein hsp90 and two immunophilins: the FK506-binding protein FKBP59 and the CsA-binding protein cyclophilin 40 (CYP40). Two sep. immunophilin-hsp90 complexes are present in LMCAT cells: one containing CYP40-hsp90, the other FKBP59-hsp90. Thus, both FKBP59 and CYP40 can be classified as hsp-binding immunophilins, and their possible involvement as

targets of immunosuppressants potentiating the GR-mediated transcriptional activity is discussed.

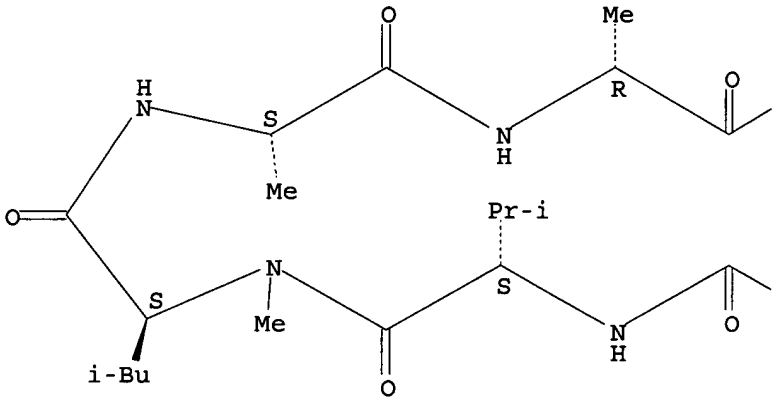
IT **156047-28-8**, SDZ 220384
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(immunosuppressant cyclosporin A potentiates the dexamethasone-induced chloramphenicol acetyltransferase gene and role for different heat shock protein-binding immunophilins in glucocorticosteroid receptor-mediated gene expression)

RN 156047-28-8 HCAPLUS

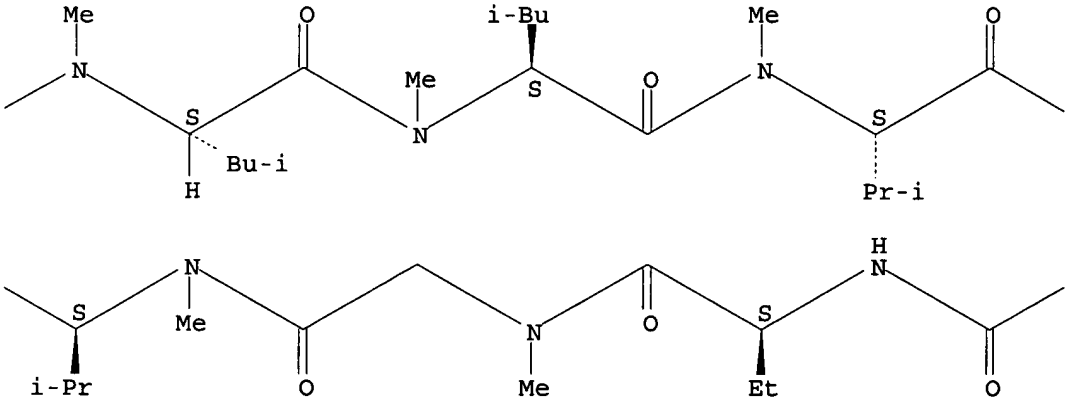
CN Cyclosporin A, 9-(N-methyl-L-valine)- (9CI) (CA INDEX NAME)

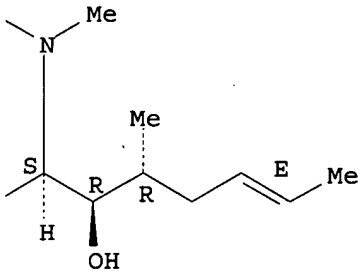
Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B





L24 ANSWER 31 OF 43 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:440571 HCAPLUS
DOCUMENT NUMBER: 122:230219
TITLE: Mode of action of SDZ NIM 811, a nonimmunosuppressive cyclosporin A analog with activity against human immunodeficiency virus (HIV) type 1: interference with HIV protein-cyclophilin A interactions
AUTHOR(S): Billich, Andreas; Hammerschmid, Franz; Peichl, Peter; Wenger, Roland; Zenke, Gerhard; Quesniaux, Valerie; Rosenwirth, Brigitte
CORPORATE SOURCE: Sandoz Forschungsinstitut GmbH, Vienna, Austria
SOURCE: Journal of Virology (1995), 69(4), 2451-61
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cyclosporins, in particular the nonimmunosuppressive derivative SDZ NIM 811, exhibit potent anti-human immunodeficiency virus type 1 (HIV-1) activity in vitro. SDZ NIM 811 interferes at two stages of the viral replication cycle: (i) translocation of the preintegration complex to the nucleus and (ii) production of infectious virus particles. Immunosuppressive activity is not correlated with anti-HIV-1 activity of cyclosporins. However, binding to cyclophilin A, the major cellular receptor protein of cyclosporins, is a prerequisite for HIV inhibition: all structural changes of the cyclosporin A mol. leading to loss of affinity to cyclophilin abolished the antiviral effect. Cyclosporin derivs. did not interact directly with HIV-1 proteins; cyclophilin was the only detectable receptor protein for antivirally active cyclosporins. There is no evidence that inhibition of HIV occurs via a gain of function of cyclophilin in the presence of cyclosporins: the complex of cyclophilin A with SDZ NIM 811 does not bind to calcineurin or to any other viral or cellular proteins under conditions in which calcineurin binding to the cyclophilin A-cyclosporin A complex is easily detectable. Thus, the loss of function caused by binding of cyclosporins to cyclophilin seems to be sufficient for the anti-HIV effect. Cyclophilin A was demonstrated to bind to HIV-1 p24gag, and the formation of complexes was blocked by cyclosporins with 50% inhibitory concns. of about 0.7 μM. HIV-2 and simian immunodeficiency virus are only weakly or not at all inhibited by cyclosporins. For gag-encoded proteins derived from HIV-1, HIV-2, or simian immunodeficiency virus particles, cyclophilin-binding capacity correlated with sensitivity of the viruses to inhibition by cyclosporins. Cyclophilin A also binds to HIV-1 proteins other than gag-encoded proteins, namely, p17gag, Nef, Vif, and

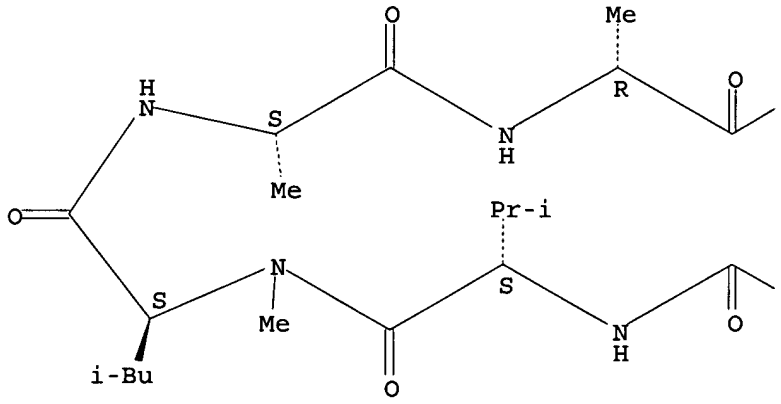
gp120env, the biol. significance of these interactions is questionable. We conclude that HIV-1 GAG-cyclophilin A interaction may be essential in HIV-1 replication, and interference with this interaction may be the mol. basis for the antiviral activity of cyclosporins.

IT **156047-28-8**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(HIV protein-cyclophilin A interactions and antiviral action of nonimmunosuppressive cyclosporin A analog SDZ NIM 811 against HIV-1)

RN 156047-28-8 HCAPLUS
CN Cyclosporin A, 9-(N-methyl-L-valine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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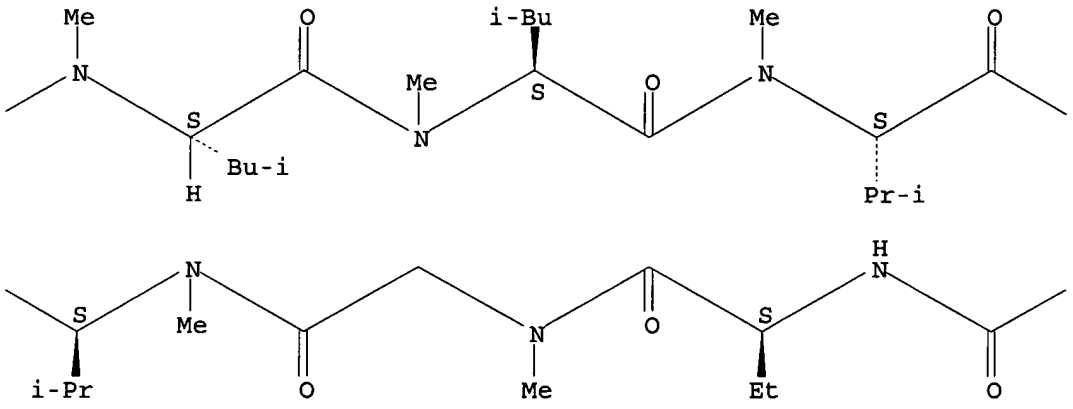
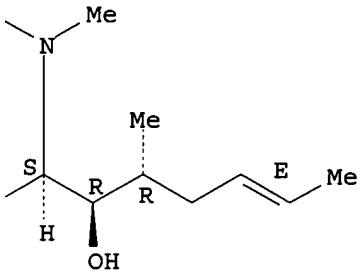




L24 ANSWER 32 OF 43 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:294145 HCAPLUS
DOCUMENT NUMBER: 122:185334
TITLE: Homogeneous immunoassays using conjugates of analytes and substituted analogs of glucose-6-phosphate dehydrogenases
INVENTOR(S): Jakobovits, Edward B.; Silen, Joy L.; Levy, Mark J.; Goodman, Thomas C.; Becker, Martin J.; Ullman, Edwin F.; Caldwell, Robert M.; Bott, Richard R.; Barnett, Christopher Charles
PATENT ASSIGNEE(S): Syntex (U.S.A.) Inc., USA; Genencor International Inc.
SOURCE: PCT Int. Appl., 121 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

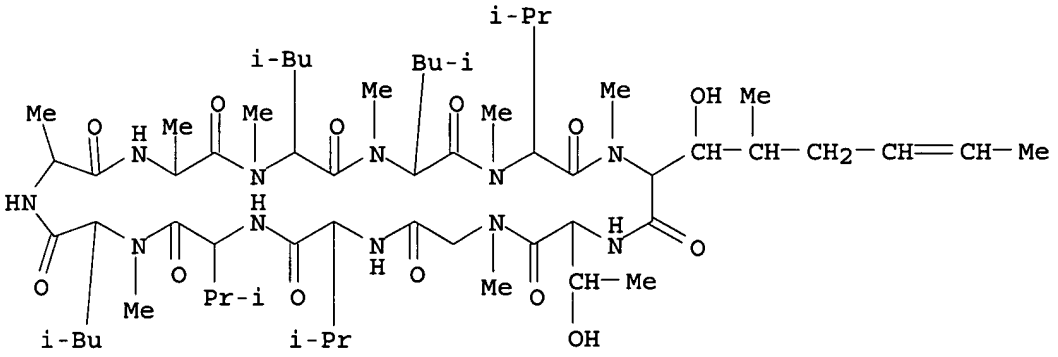
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9424559	A2	19941027	WO 1994-US3437	19940407
WO 9424559	A3	19950126		
W: CA, FI, JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 6455288	B1	20020924	US 1993-44857	19930408
CA 2160115	AA	19941027	CA 1994-2160115	19940407
EP 710360	A1	19960508	EP 1994-923147	19940407
EP 710360	B1	19991110		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
JP 08510638	T2	19961112	JP 1994-523227	19940407
AT 186598	E	19991115	AT 1994-923147	19940407
ES 2139087	T3	20000201	ES 1994-923147	19940407
US 6033890	A	20000307	US 1995-445463	19950522
US 6090567	A	20000718	US 1995-445464	19950522
PRIORITY APPLN. INFO.:			US 1993-44857 A	19930408
			WO 1994-US3437 W	19940407

AB Immunoassays using mutant forms of glucose-6-phosphate dehydrogenase (G6PDH) as labels are described. In particular, the assays use conjugates of an analyte or analyte analog and a mutant NAD+-dependent G6PDH. Typically, the mutations involve deletion or substitution of lysine residues or introduction of cysteine residues. The preparation of such analogs of Leuconostoc G6PDH by site-directed mutagenesis and expression of the

cloned genes and the conjugation of analytes to the enzyme analogs are described. Assays for antibodies to analytes that measured the inhibition of G6PDH conjugated with the analytes by the antibodies are described.

IT **108027-43-6**, Cyclosporins
RL: ANT (Analyte); ANST (Analytical study)
(immunoanal. determination of; homogeneous immunoassays using conjugates of analytes and substituted analogs of glucose-6-phosphate dehydrogenases)

RN 108027-43-6 HCAPLUS
CN Cyclosporin S (9CI) (CA INDEX NAME)



L24 ANSWER 33 OF 43 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:178766 HCAPLUS
DOCUMENT NUMBER: 122:563
TITLE: Evidence that the inhibition of Na+/K+-ATPase activity by FK506 involves calcineurin
AUTHOR(S): Lea, Janice P.; Sands, Jeff M.; McMahon, Steven J.; Tumlin, James A.
CORPORATE SOURCE: Department Medicine, Emory University School Medicine, Atlanta, GA, USA
SOURCE: Kidney International (1994), 46(3), 647-52
CODEN: KDYIA5; ISSN: 0085-2538
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We reported that cyclosporin A (CsA) inhibits Na+/K+-ATPase activity in specific segments of the rat nephron. In this study, we tested the hypothesis that cyclosporin A reduces Na+/K+-ATPase activity through inhibition of calcineurin. In T cells, cyclosporin A and FK506 bind to immunophilins and inhibit the phosphatase activity of calcineurin; Rapamycin and SDZ 220-384 also bind to immunophilins but do not change calcineurin activity. Na+/K+-ATPase activity was measured in microdissected rat proximal tubule (S2 subsegment), medullary thick ascending limb (mTAL), and cortical collecting duct (CCD). First we found that two inhibitors of calcineurin, pentafluorophenol (PFP, 100 mM) and peptide 412 (1 mM), significantly reduced Na+/K+-ATPase activity in the CCD by 78% and 70%, resp. In CCDs, FK506 inhibited Na+/K+-ATPase activity by 61 to 85% at concns. of 1.5 to 6 ng/mL, but not at 0.5 ng/mL. FK506 (6 ng/mL) inhibited Na+/K+-ATPase activity in mTALs by 56% but did not inhibit it in S2s or glomeruli. In contrast, Rapamycin (12.5 ng/mL) did not change Na+/K+-ATPase activity in CCDs or mTALs, but at a concentration of 12.5 μg/mL did block the inhibitory effect of FK506 (6 ng/mL) in both segments. SDZ 220-384 (600 ng/mL) did not change Na+/K+-ATPase activity in CCDs. Thus, in CCDs and mTALs: (1) FK506, like cyclosporin A, inhibits Na+/K+-ATPase activity; (2) Rapamycin and SDZ 220-384 do not inhibit

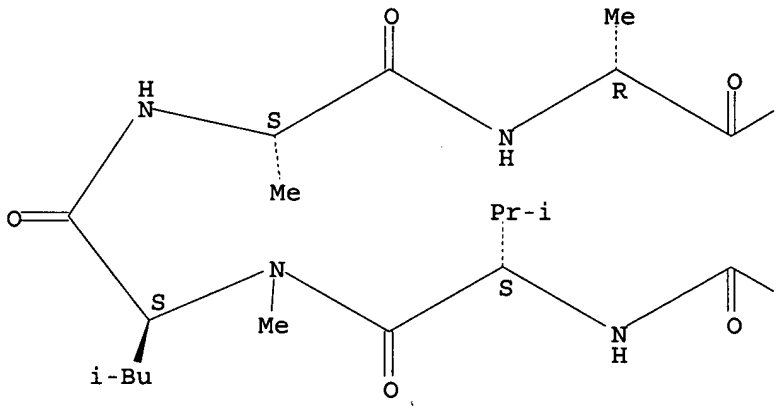
Na+/K+-ATPase activity; and (3) Rapamycin prevents FK506-induced inhibition of Na+/K+-ATPase activity. These responses may be explained by a direct inhibition of calcineurin activity yielding lower Na+/K+-ATPase activity in CCDs and mTALs.

IT **156047-28-8**, SDZ 220-384
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(rapamycin and SDZ 220-384 noninhibition of Na+/K+-ATPase activity in nephron in relation to calcineurin activity nonmediation)

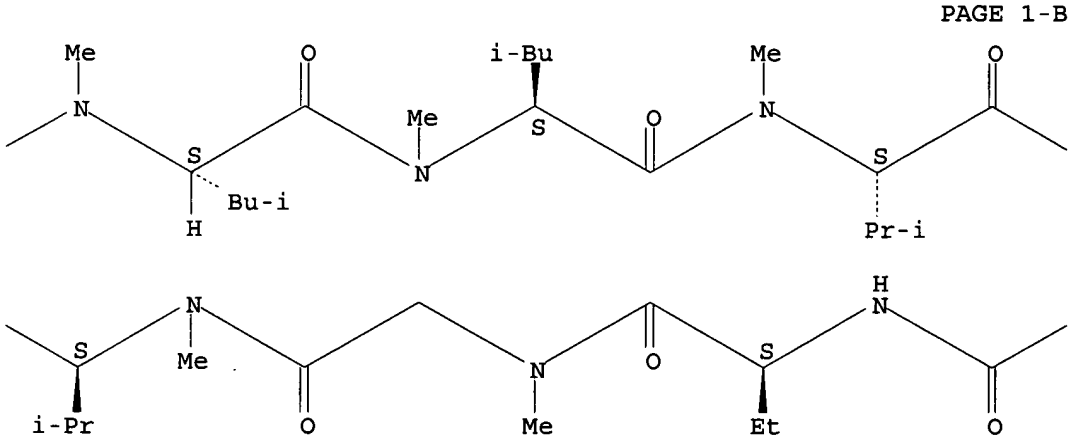
RN 156047-28-8 HCAPLUS
CN Cyclosporin A, 9-(N-methyl-L-valine)- (9CI) (CA INDEX NAME)

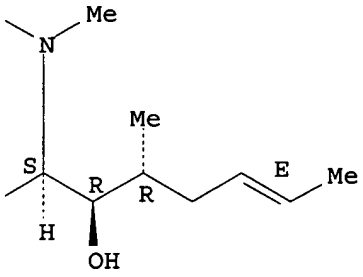
Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B





L24 ANSWER 34 OF 43 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:51474 HCAPLUS
DOCUMENT NUMBER: 122:45734
TITLE: Roles of peptidyl-prolyl cis-trans isomerase and calcineurin in the mechanisms of antimalarial action of cyclosporin A, FK506, and rapamycin
AUTHOR(S): Bell, Angus; Wernli, Barbara; Franklin, Richard M.
CORPORATE SOURCE: Dep. Structural Biology, Univ. Basal, Basel, CH-4056, Switz.
SOURCE: Biochemical Pharmacology (1994), 48(3), 495-503
CODEN: BCPCA6; ISSN: 0006-2952
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The immunosuppressive peptide cyclosporin A inhibits the growth of malaria parasites in vitro and in vivo, but little is known about its mechanism of antimalarial action. The immunosuppressive action of cyclosporin A is believed to result from binding of the drug to cytophilins (intracellular peptidyl-prolyl cis-trans isomerases), and inhibition of the protein phosphatase calcineurin by the cyclosporin A-cyclophilin complex. Two immunosuppressive macrolides, FK506 and rapamycin, bind to a distinct isomerase, FKBP12, and the FK506-FKBP complex also inhibits calcineurin. Calcineurin itself is apparently involved in signal transduction between the T-cell membrane and nucleus, and its inhibition blocks T-cell activation. Rapamycin inhibits a later step in T-cell proliferation. Peptidylprolyl cis-trans isomerase activity was detected in exts. of Plasmodium falciparum. It was completely inhibited by concns. of cyclosporin A above 0.1 μM, but not by FK506 or rapamycin, and probably represented one or more cyclophilins. Comparison of the antimalarial and anti-isomerase activities of a series of cyclosporin analogs failed to reveal a correlation between the two properties. Cyclosporin A and its more active 8'-oxymethyl-dihydro-derivative, in combination with the cyclophilin-containing P. falciparum extract inhibited the protein phosphatase activity of bovine calcineurin. Therefore inhibition of a putative P. falciparum calcineurin by a complex of CsA and cyclophilin might be responsible for the antimalarial action of the drug. The most active cyclosporin, however, was a 3'-keto-derivative of cyclosporin D (SDZ PSC-833) which inhibited P. falciparum growth with a 50% inhibitory concns. (IC50) of 0.032 μM (compared with 0.30 μM for cyclosporin A), but was a poor inhibitor of the parasite isomerase. 3'-Keto-cyclosporin D has negligible immunosuppressive activity, but it strongly inhibits the P-glycoprotein of multi-drug resistant mammalian tumor cells. FK506 and rapamycin were also active antimalarials (IC50 of 1.9 and 2.6 μM,

resp.) but in the absence of detectable FKBP in P. falciparum exts., their mechanisms of antimalarial action remain unclear.

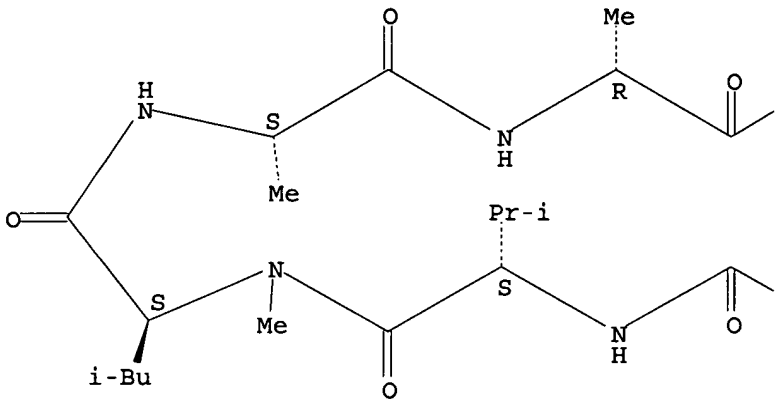
IT **156047-28-8**
RL: BIOL (Biological study)
(peptidyl-prolyl cis-trans isomerase inhibition by, antimalarial activity in relation to)

RN 156047-28-8 HCAPLUS

CN Cyclosporin A, 9-(N-methyl-L-valine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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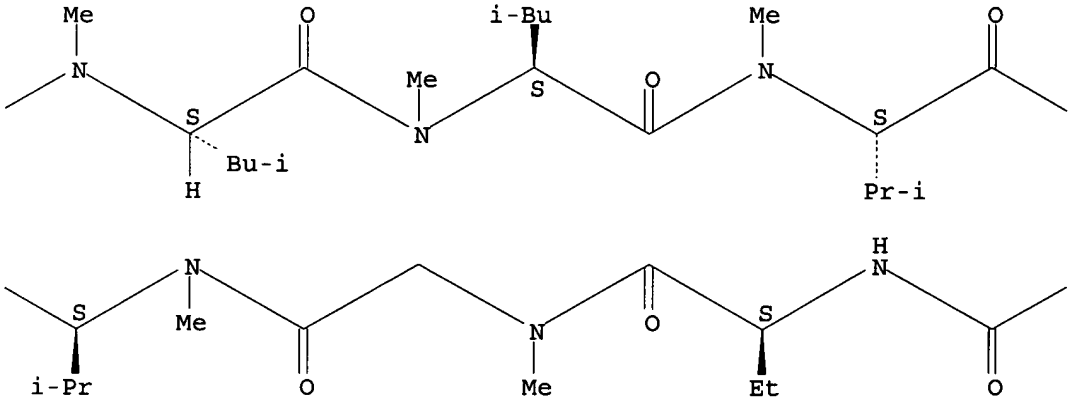
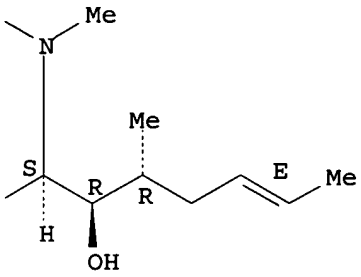




L24 ANSWER 35 OF 43 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1994:645147 HCAPLUS
DOCUMENT NUMBER: 121:245147
TITLE: Structure-activity relationships for the interaction between cyclosporin A derivatives and the Fab fragment of a monoclonal antibody
AUTHOR(S): Rauffer, Nathalie; Zeder-Lutz, Gabrielle; Wenger, Roland; Van Regenmortel, Marc H. V.; Altschuh, Daniele
CORPORATE SOURCE: Inst. Biol. Mol. Cell., CNRS, Strasbourg, 67084, Fr.
SOURCE: Molecular Immunology (1994), 31(12), 913-22
CODEN: MOIMD5; ISSN: 0161-5890
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The crystallog. structure of a complex between cyclosporin A (CS) and the Fab fragment of monoclonal antibody R45-45-11 has been solved to 2.65 Å resolution, yielding a precise three-dimensional picture of interacting surfaces. In order to evaluate the contribution of observed contacts to the energy of interaction, we have measured the effect on binding affinity of minor chemical modifications of CS. The equilibrium binding constant of the Fab fragment for a set of cyclosporin analogs was obtained by measuring in a biosensor instrument the dependence of complex formation on Fab concentration, at constant analog concns. Data were analyzed using Scatchard plots. Differences in binding energy resulting from cyclosporin modifications discriminated between two types of contact areas. The first type displays adaptability to structural modifications of cyclosporin at the cost of a small decrease in binding energy, and contacting residues in the antibody form the periphery of the combining site. The second type does not accommodate structural changes and corresponds in cyclosporins to three residues whose modifications drastically decrease binding energy with the antibody. The corresponding contact residues in the antibody form the core of the antibody combining site.

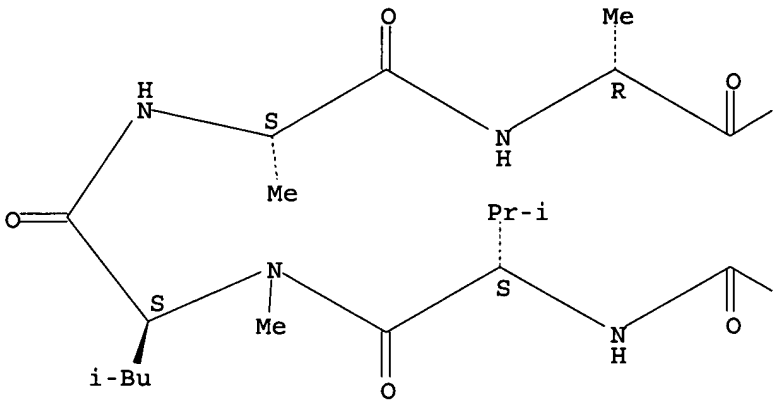
IT **156047-28-8**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(structure-activity relationships for interaction between cyclosporin A derivs. and the Fab fragment of monoclonal antibody)

RN 156047-28-8 HCAPLUS
CN Cyclosporin A, 9-(N-methyl-L-valine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry as shown.

PAGE 1-A



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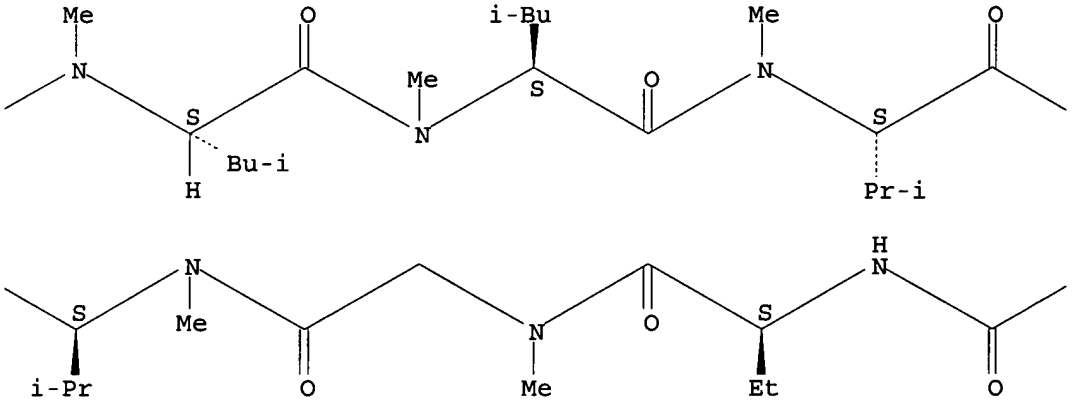
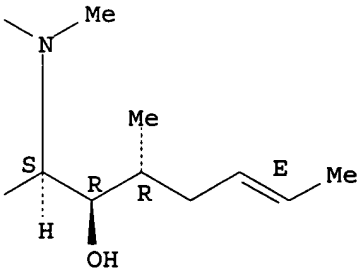


PAGE 1-C



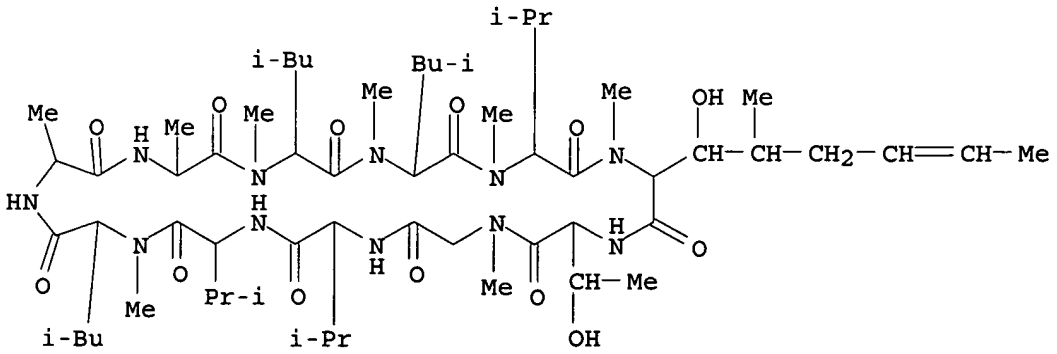
L24 ANSWER 36 OF 43 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1994:564006 HCAPLUS
DOCUMENT NUMBER: 121:164006
TITLE: Pharmaceutical compositions including a drug, a crosslinked polymeric substance, an oil, and a surface active agent.
INVENTOR(S): Carli, Fabio; Lombardi, Daniela; Esposito, Pierandrea; Dobetti, Luca; Boltri, Luigi
PATENT ASSIGNEE(S): Vectorpharma International S.P.A., Italy
SOURCE: Eur. Pat. Appl., 12 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 598337	A2	19940525	EP 1993-118278	19931111
EP 598337	A3	19950614		
EP 598337	B1	19990414		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, PT				
AT 178787	E	19990415	AT 1993-118278	19931111
ES 2132162	T3	19990816	ES 1993-118278	19931111
US 6107276	A	20000822	US 1997-997463	19971223
PRIORITY APPLN. INFO.:			IT 1992-MI2603 A	19921113
			US 1993-150227 B1	19931110
			US 1995-528597 A1	19950915

AB Pharmaceutical compns. including a slightly soluble drug incorporated in a water-swellable, but water-insol. cross-linked polymer, a surface active agent, and an oil show much improved dissoln. and, consequently, bioavailability in respect to the drug as is or used with a polymeric carrier of said type. Ubidecarenone was dissolved in a 50% mixture of Lexol PG 865 and Tween 80 and the solution thus obtained was added at 50° to crospovidone so as to secure a drug/polymer ratio equal to 1:3 by weight and the product obtained was allowed to stand at room temperature for 24 h.

IT **108027-43-6**, Cyclosporins
RL: BIOL (Biological study)
(pharmaceutical compns. containing crosslinked polymers and oils and surfactants and)

RN 108027-43-6 HCAPLUS
CN Cyclosporin S (9CI) (CA INDEX NAME)



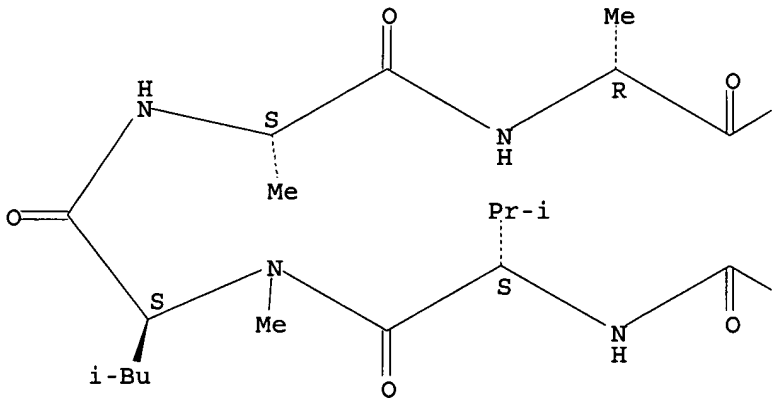
L24 ANSWER 37 OF 43 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1994:449599 HCAPLUS
DOCUMENT NUMBER: 121:49599
TITLE: Calcineurin has a very tight-binding pocket for the side chain of residue 4 of cyclosporin
AUTHOR(S): Papageorgiou, Christos; Borer, Xaver; French, Richard R.
CORPORATE SOURCE: Preclin. Res., Sandoz Pharma Ltd., Basle, CH-4002, Switz.
SOURCE: Bioorganic & Medicinal Chemistry Letters (1994), 4(2), 267-72
CODEN: BMCLE8; ISSN: 0960-894X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Derivs. of cyclosporin A (CsA) at position 4 were synthesized to probe the interaction of the CsA/CypA complex with calcineurin (CaN). Both lipophilic and hydrophilic substituents are detrimental for the immunosuppressive activity, indicating that CaN has a very "tight-binding pocket" for this region.

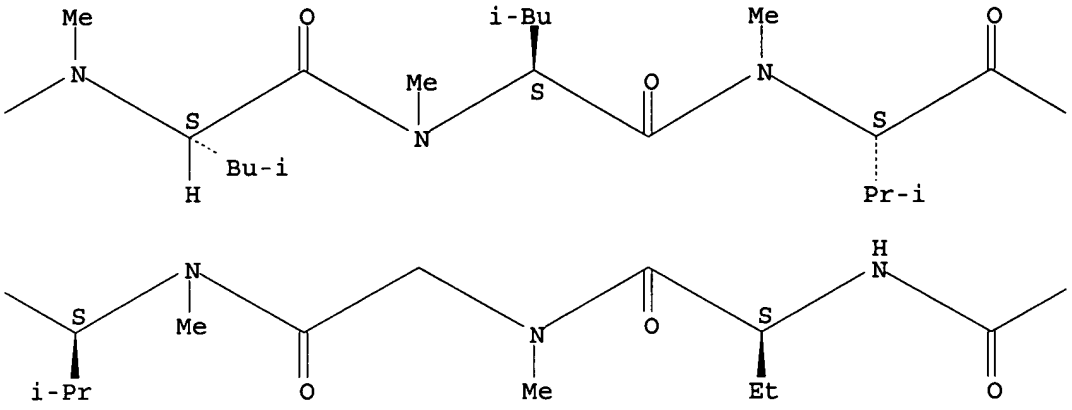
IT **156047-28-8P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and immunosuppressive activity of, structure in relation to)
RN 156047-28-8 HCAPLUS
CN Cyclosporin A, 9-(N-methyl-L-valine)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



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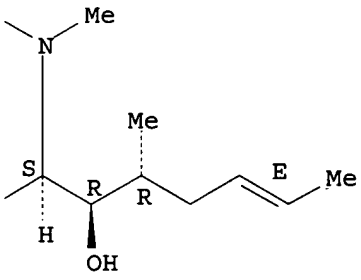


L24 ANSWER 38 OF 43 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1992:648314 HCAPLUS
DOCUMENT NUMBER: 117:248314
TITLE: Enzymic biosynthesis of cyclosporin A and analogs
AUTHOR(S): Lawen, A.; Dittmann, J.; Schmidt, B.; Riesner, D.; Kleinkauf, H.
CORPORATE SOURCE: Inst. Biochem. Mol. Biol., Tech. Univ. Berlin, Berlin, D-W-1000/10, Germany
SOURCE: Biochimie (1992), 74(5), 511-16
CODEN: BICMBE; ISSN: 0300-9084
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The final assembly of the undecapeptide chain of cyclosporin A and its cyclization is accomplished in Beauveria nivea by cyclosporin synthetase. This multienzyme is the largest integrated enzyme structure so far reported. Its size has been estimated at approx. 1400 kDa by two different methods: (1), by 3% SDS-PAGE using the related multienzymes ACV synthetase and gramicidin S synthetase 2 as refs. (420 and 556 kDa, resp.), and (2), by CsCl d. gradient centrifugation expts. using fluorescence-labeled cyclosporin synthetase. Besides cyclosporin A and a number of cyclosporins known from fermentation studies cyclosporin synthetase is capable of

synthesizing some new cyclosporins which are so far unobtainable by fermentation

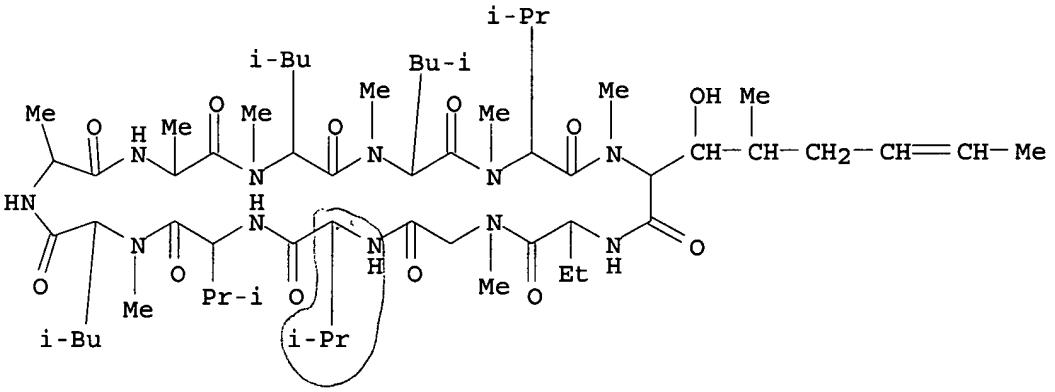
For example the synthesis of [N-methyl-(+)-2-amino-3-hydroxy-4,4-dimethyloctanoic acid1]CyA, dihydro-CyA, [L-norvaline2,5, N-methyl-L-norvaline11]CyA, [L-allo-isoleucine5, N-methyl-L-allo-sioleucine11]CyA, [D-2-aminobutyric acid8]CyA, [β-chloro-D-alanine8]CyA and some related compds. could be established. By using a related but different enzyme from Cylindrotrichum Bonorden, the peptolide [L-threonine2, L-leucine5,10, D-2-hydroxyisovaleric acid8]CyA could be synthesized in vitro. These cyclosporins were synthesized in sufficient quantities to examine their structure by FAB mass spectroscopy and explore their immunosuppressivity. All new cyclosporins so far synthesized in the in vitro system are immunosuppressive.

IT **108027-42-5**

RL: FORM (Formation, nonpreparative)
(formation of, by cyclosporin synthetase from Beauveria nivea)

RN 108027-42-5 HCAPLUS

CN Cyclosporin Q (9CI) (CA INDEX NAME)



L24 ANSWER 39 OF 43 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER:	1992:136281 HCAPLUS
DOCUMENT NUMBER:	116:136281
TITLE:	Formulation of hydrophobic and/or lipophilic peptide drugs
INVENTOR(S):	Dauth, Christoph; Decker, Karl Ludwig; Geissler, Sabine; Heidenbluth, Karlheinz; Hempel, Roland; Hoffmann, Evelyn; Poetter, Heinrich; Rattke, Wilfried; Rudat, Wolf Ruediger; et al.
PATENT ASSIGNEE(S):	Arzneimittelwerk Dresden G.m.b.H., Germany
SOURCE:	Ger. (East), 4 pp. CODEN: GEXXA8
DOCUMENT TYPE:	Patent
LANGUAGE:	German
FAMILY ACC. NUM. COUNT:	1

PATENT INFORMATION:

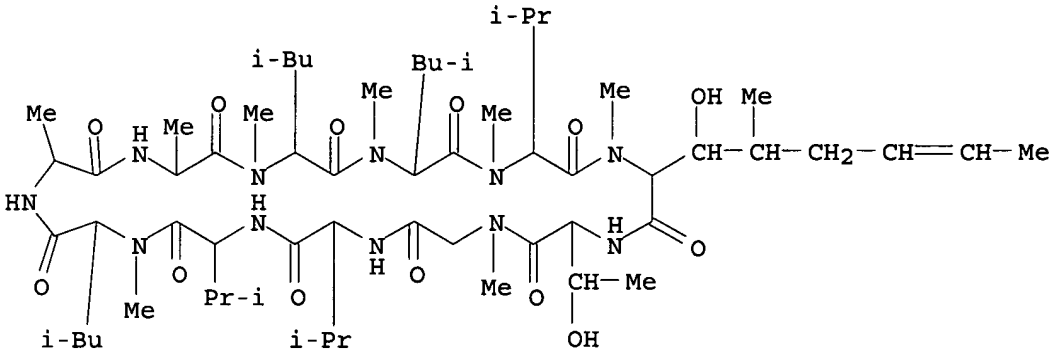
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DD 295765	A5	19911114	DD 1988-318014	19880718
PRIORITY APPLN. INFO.:			DD 1988-318014	19880718

AB Solns. of hydrophobic and/or lipophilic peptide drugs, such as cyclosporins, are blended into water or aqueous solns. of surfactants, low mol.-weight carbohydrates, salts, etc. The precipitate obtained, optionally

lyophilized, is incorporated into a hydrophilic polymer matrix. A solution of 100g cyclosporin A in 1 L EtOH was blended into 5 L aqueous 0.5% NH4AcO solution, to give a precipitate which was lyophilized and homogenized, at 45°, with 250 mL of an aqueous solution of 1% agar, and 0.5% Tween 40. Cooling of the mixture gave a gel, which was homogenized and filled into gelatin capsules.

IT **108027-43-6**
RL: PROC (Process)
(formulation of)

RN 108027-43-6 HCAPLUS
CN Cyclosporin S (9CI) (CA INDEX NAME)



L24 ANSWER 40 OF 43 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1990:538498 HCAPLUS
DOCUMENT NUMBER: 113:138498
TITLE: Cyclosporin-containing topical drug composition for treatment of autoimmune skin diseases
INVENTOR(S): Elias, Peter M.
PATENT ASSIGNEE(S): Sandoz-Patent-G.m.b.H., Fed. Rep. Ger.
SOURCE: Ger. Offen., 13 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 3915617	A1	19891116	DE 1989-3915617	19890512
CH 679119	A	19911231	CH 1989-1735	19890509
GB 2218334	A1	19891115	GB 1989-10707	19890510
GB 2218334	B2	19911002		
FR 2631235	A1	19891117	FR 1989-6463	19890512
JP 02017127	A2	19900122	JP 1989-120234	19890512
JP 07005473	B4	19950125		
BE 1002266	A5	19901113	BE 1989-520	19890512
US 5807820	A	19980915	US 1995-446984	19950522
PRIORITY APPLN. INFO.:			GB 1988-11357 A	19880513
			GB 1988-24779 A	19881021
			US 1989-350952 B1	19890511
			US 1991-743846 B1	19910812
			US 1992-856133 B1	19920323
			US 1993-138561 B1	19931018

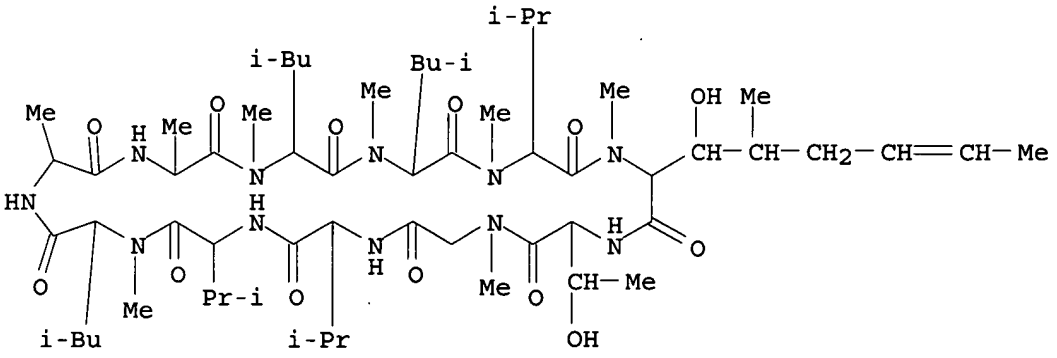
OTHER SOURCE(S): MARPAT 113:138498

AB Compns. for the topical treatment of autoimmune disease and for hair growth stimulation comprise a cyclosporin and a (poly)unsatd. C12-24 fatty acid or alc. The composition are useful for the treatment of psoriasis, dermatitis and alopecia. A composition comprised cyclosporin A 20, vaccenyl alc. 20, iso-PrOH 40 and Tween-80 20. Cyclosporin A showed higher in-vitro penetration into the rat skin from this composition than from a composition lacking vaccenyl alc.

IT **108027-43-6**, Cyclosporins
RL: BIOL (Biological study)
(skin diseases treatment by compns. containing fatty acids or alcs. and)

RN 108027-43-6 HCAPLUS

CN Cyclosporin S (9CI) (CA INDEX NAME)



L24 ANSWER 41 OF 43 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1990:4323 HCAPLUS

DOCUMENT NUMBER: 112:4323

TITLE: Cell-free biosynthesis of new cyclosporins

AUTHOR(S): Lawen, Alfons; Traber, Rene; Geyl, Dieter; Zocher, Rainer; Kleinkauf, Horst

CORPORATE SOURCE: Inst. Biochem. Mol. Biol., Tech. Univ. Berlin, Berlin, D-1000/10, Fed. Rep. Ger.

SOURCE: Journal of Antibiotics (1989), 42(8), 1283-9
CODEN: JANTAJ; ISSN: 0021-8820

DOCUMENT TYPE: Journal

LANGUAGE: English

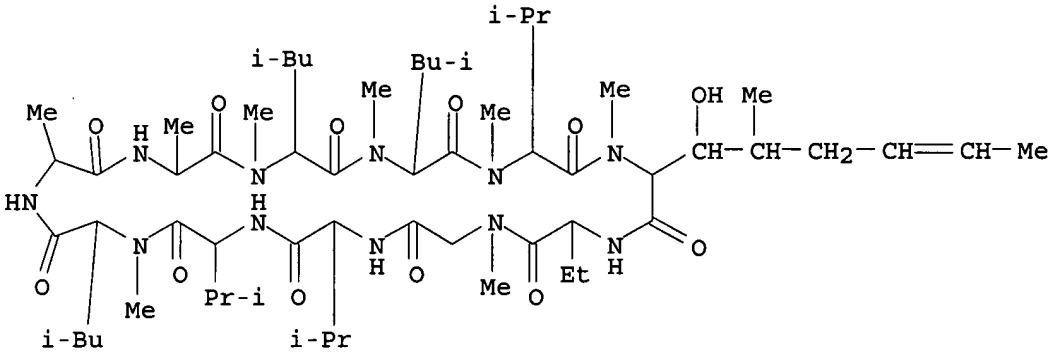
AB An enzyme preparation, isolated from exts. of the fungus Beauveria nivea (previously designated Tolypocladium inflatum), is used to synthesize cyclosporins (Cy's) in vitro. At suboptimal temperature it was possible to obtain about 50 μg of CyA per mL. The enzyme also produces several of the naturally occurring congeners of CyA, such as the Cy's B, C, D, G, M, O, Q, U and V and some of the analogs known to be produced by the fungus via precursor directed biosynthesis, like dihydro-CyA, [N-methyl-L-β-cyclohexylalanine1]CyA, [t-allylglycine2]CyA and [D-serine8]CyA. Furthermore, Cy's not obtainable by the fungus could be prepared by the enzyme system in the presence of the appropriate precursor amino acids; the synthesis of [N-methyl-(+)-2-amino-3-hydroxy-4,4-dimethyloctanoic acid1]CyA, [L-norvaline2,5, N-methyl-L-norvaline11]CyA, [L-norvaline5, N-methyl-L-norvaline11]CyA, [L-allo-isoleucine5, N-methyl-L-allo-isoleucine11]CyA, [L-allo-isoleucine5,11]CyA, [D-2-aminobutyric acid9]CyA and [β-chloro-D-alanine8]CyA could be established. The immunosuppressive effects of the new derivs. are

discussed.

IT **108027-42-5**, Cyclosporin Q
RL: PROC (Process)
(biosynthesis of, Beauveria nivea enzyme exts. in)

RN 108027-42-5 HCAPLUS

CN Cyclosporin Q (9CI) (CA INDEX NAME)



L24 ANSWER 42 OF 43 HCAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1988:126908 HCAPLUS

DOCUMENT NUMBER: 108:126908

TITLE: Immunochemical study of cyclosporin conformation in aqueous medium

AUTHOR(S): Quesniaux, V. F. J.; Wenger, R. M.; Schreier, M. H.; Van Regenmortel, M. H. V.

CORPORATE SOURCE: Lab. Immunochim., Inst. Biol. Mol. Cell., Strasbourg, 67084, Fr.

SOURCE: Protides of the Biological Fluids (1987), 35, 507-10
CODEN: PBFPA6; ISSN: 0079-7065

DOCUMENT TYPE: Journal

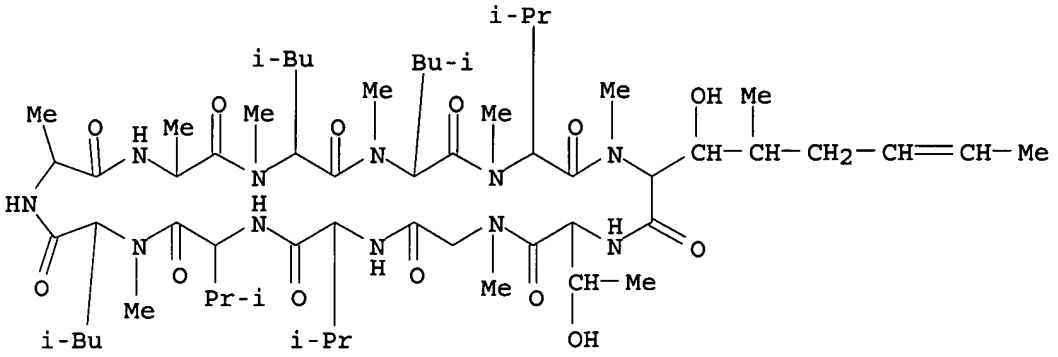
LANGUAGE: English

AB The fine specificity of monoclonal antibodies for different residues of cyclosporins (Cs) was studied. The conformation of Cs in aqueous medium corresponds to that observed in crystals rather than that found in aprotic solvents.

IT **108027-43-6**, Cyclosporins
RL: PRP (Properties)
(conformation of, in crystalline state vs. aqueous solution, immunochem. anal. in)

RN 108027-43-6 HCAPLUS

CN Cyclosporin S (9CI) (CA INDEX NAME)

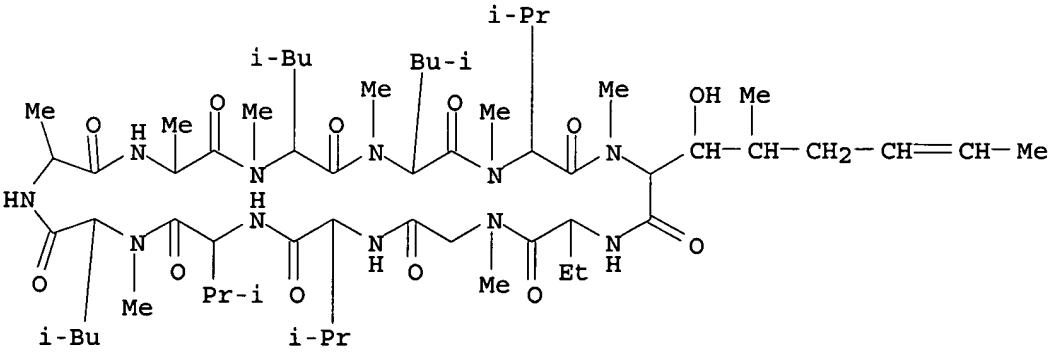


L24 ANSWER 43 OF 43 HCAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1987:210631 HCAPLUS
DOCUMENT NUMBER: 106:210631
TITLE: Novel cyclosporins from Tolypocladium inflatum. Cyclosporins K-Z
AUTHOR(S): Traber, Rene; Hofmann, Hans; Loosli, Hans Rudolf; Ponelle, Monique; Von Wartburg, Albert
CORPORATE SOURCE: Praeklin. Forsch., Sandoz A.-G., Basel, CH-4002, Switz.
SOURCE: Helvetica Chimica Acta (1987), 70(1), 13-36
CODEN: HCACAV; ISSN: 0018-019X
DOCUMENT TYPE: Journal
LANGUAGE: German

AB The isolation of and structure of 16 new cyclosporins (K-Z) are reported. The structural assignments of these novel congeners are based on chemical degradation, correlation reactions, mass spectra, and extensive anal. of 1 H- and 13C-NMR spectra. All cyclosporins are cyclic undecapeptides differing from each other by minor variations in amino acid sequence. Comparison of the immunosuppressive and antifungal effects furnished new information concerning structure-activity relationships.

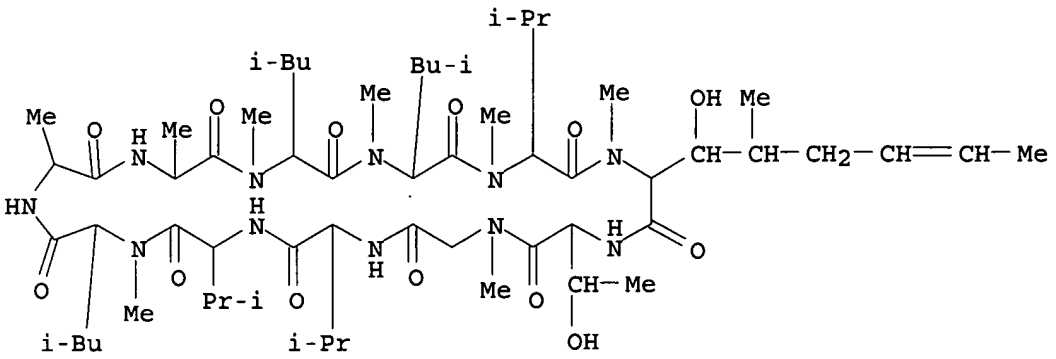
IT **108027-42-5 108027-43-6**
RL: BIOL (Biological study)
(structure and biol. activity of, from Tolypocladium inflatum)

RN 108027-42-5 HCAPLUS
CN Cyclosporin Q (9CI) (CA INDEX NAME)



RN 108027-43-6 HCAPLUS

CN Cyclosporin S (9CI) (CA INDEX NAME)



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FILE 'REGISTRY' ENTERED AT 11:38:26 ON 06 APR 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,    *
* effective March 20, 2005.  A new display format, IDERL, is now     *
* available and contains the CA role and document type information.  *
*                                                                    *
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predicted properties as well as tags indicating availability of
experimental property data in the original document. For information
on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

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L23 ANSWER 1 OF 6 REGISTRY COPYRIGHT 2006 ACS on STN
RN 603973-24-6 REGISTRY
CN Cyclo[L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl-(2S,3R,4R,6E)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoyl-(2S)-2-aminobutanoyl-N-methylglycyl-N-ethyl-L-valyl-(4S,5R)-5-methyl-2-phenyl-4-oxazolidinecarbonyl-N-methyl-L-leucyl] (9CI) (CA INDEX NAME)
NTE cyclic
modified (modifications unspecified)

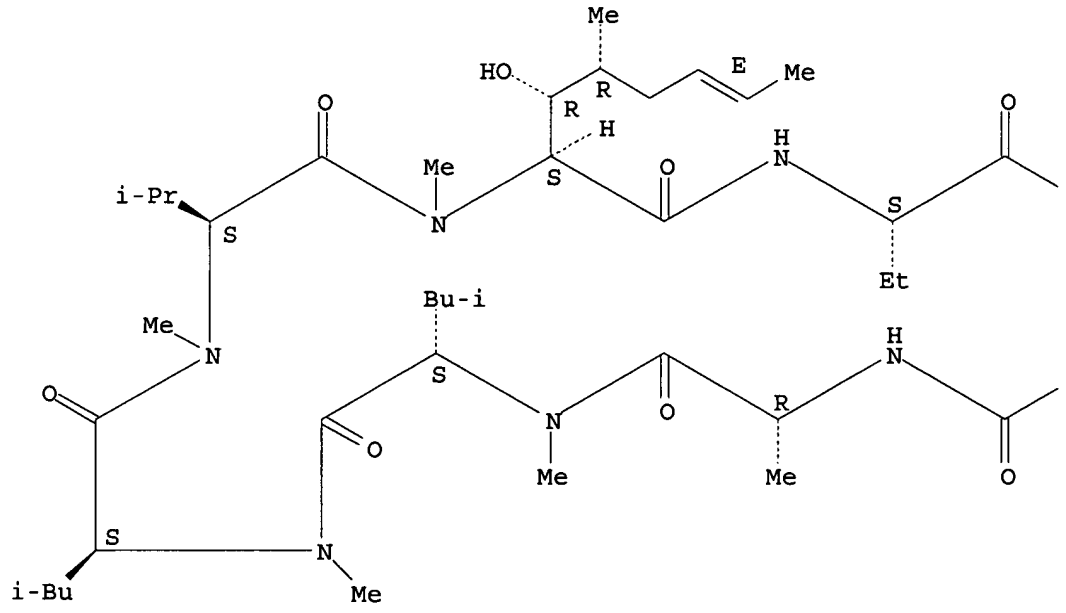
type	location		description
uncommon	Aaa-1	-	-
uncommon	Abu-2	-	-
uncommon	Sar-3	-	-
uncommon	Aaa-5	-	-
stereo	Ala-8	-	D

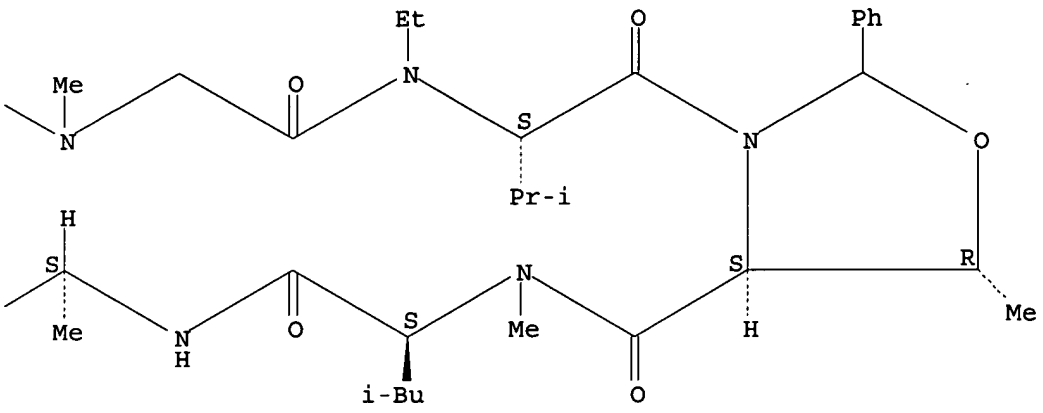
SQL 11

SEQ3 1 Aaa-Abu-Sar-Val-Aaa-Leu-Ala-Ala-Leu-Leu-
11 Val

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A





PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

REFERENCE 1: 139:261550

L23 ANSWER 2 OF 6 REGISTRY COPYRIGHT 2006 ACS on STN
RN 603973-23-5 REGISTRY
CN Cyclo[L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl-(2S,3R,4R,6E)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoyl-(2S)-2-aminobutanoyl-N-methylglycyl-N-ethyl-L-valyl-L-threonyl-N-methyl-L-leucyl] (9CI) (CA INDEX NAME)
NTE cyclic
modified (modifications unspecified)

type	location		description
uncommon	Aaa-1	-	-
uncommon	Abu-2	-	-
uncommon	Sar-3	-	-
stereo	Ala-8	-	D

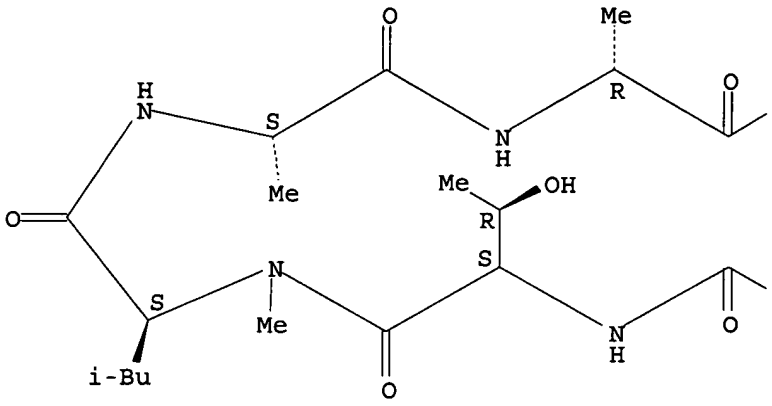
SQL 11

SEQ3 1 Aaa-Abu-Sar-Val-Thr-Leu-Ala-Ala-Leu-Leu-
11 Val

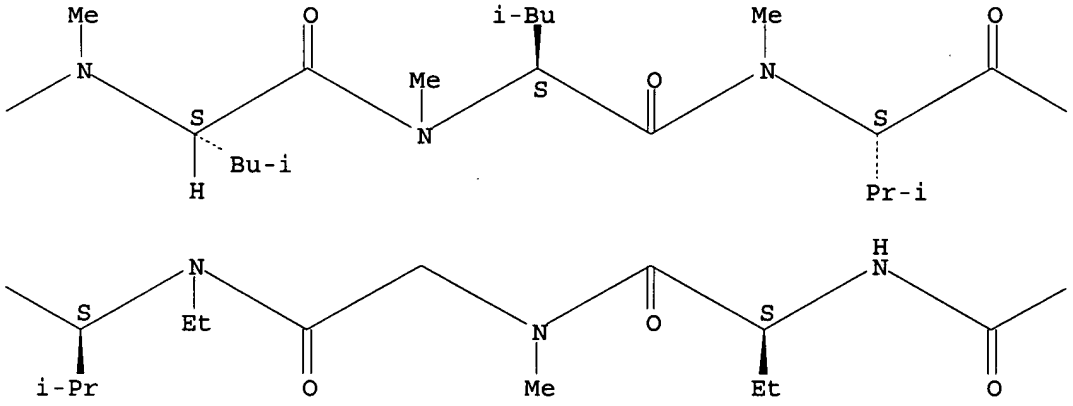
RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



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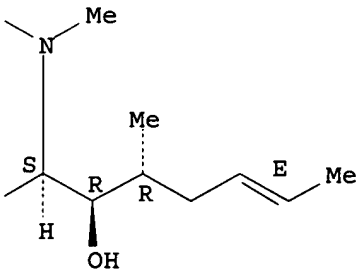


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

RELATED SEQUENCES AVAILABLE WITH SEQLINK

REFERENCE 1: 139:261550

L23 ANSWER 3 OF 6 REGISTRY COPYRIGHT 2006 ACS on STN
RN 254435-90-0 REGISTRY
CN Cyclosporin A, 9-(N-ethyl-L-valine)- (9CI) (CA INDEX NAME)
NTE cyclic
modified (modifications unspecified)

type	------ location ------		description
uncommon	Aaa-1	-	-
uncommon	Abu-2	-	-
uncommon	Sar-3	-	-
stereo	Ala-8	-	D

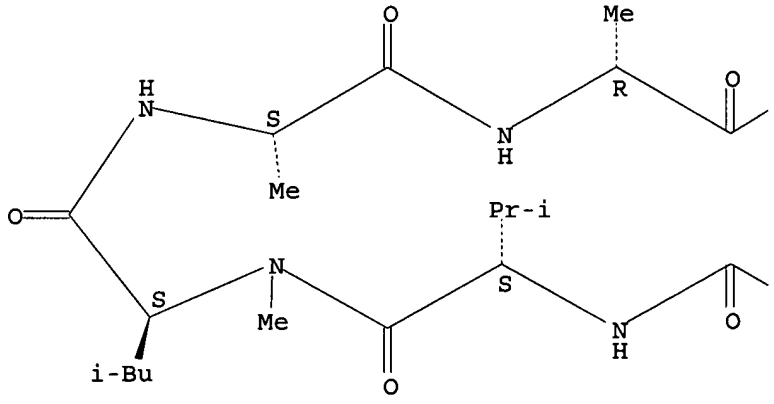
SQL 11

SEQ3 1 Aaa-Abu-Sar-Val-Val-Leu-Ala-Ala-Leu-Leu-
11 Val

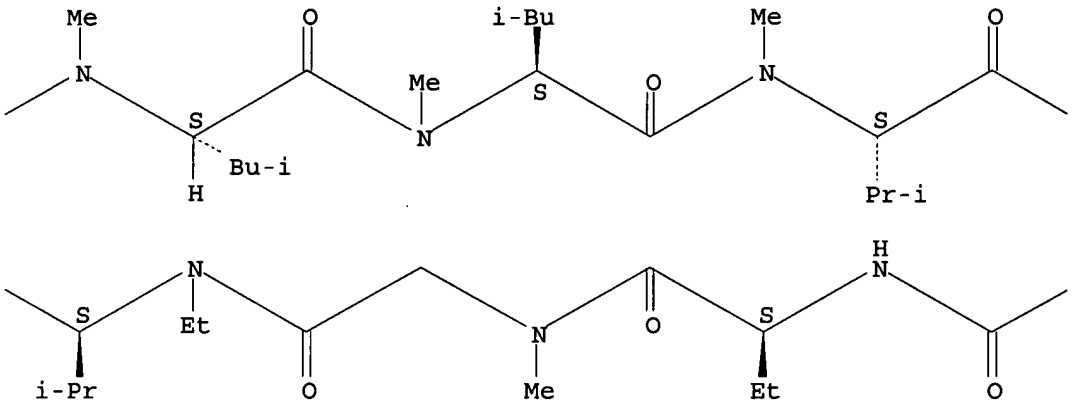
RELATED SEQUENCES AVAILABLE WITH SEQLINK

Absolute stereochemistry.
Double bond geometry as shown.

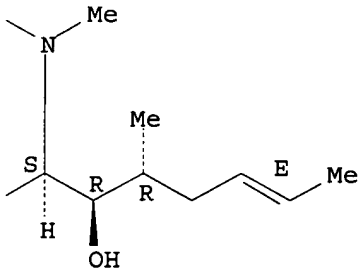
PAGE 1-A



PAGE 1-B



PAGE 1-C



RELATED SEQUENCES AVAILABLE WITH SEQLINK

REFERENCE 1: 140:53021

REFERENCE 2: 138:271939

REFERENCE 3: 133:350496

REFERENCE 4: 132:88163

L23 ANSWER 4 OF 6 REGISTRY COPYRIGHT 2006 ACS on STN
RN 156047-28-8 REGISTRY
CN Cyclosporin A, 9-(N-methyl-L-valine)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1,4,7,10,13,16,19,22,25,28,31-Undecaazacyclotritriacontane, cyclic peptide deriv.
OTHER NAMES:
CN N-Methyl-Val-4-CsA
CN SDZ 220-384
NTE cyclic

modified (modifications unspecified)

type	location		description
uncommon	Aaa-1	-	-
uncommon	Abu-2	-	-
uncommon	Sar-3	-	-
stereo	Ala-8	-	D

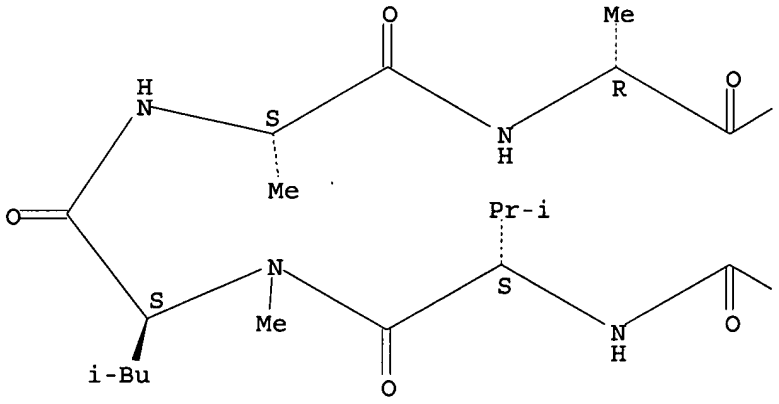
SQL 11

SEQ3 1 Aaa-Abu-Sar-Val-Val-Leu-Ala-Ala-Leu-Leu-
11 Val

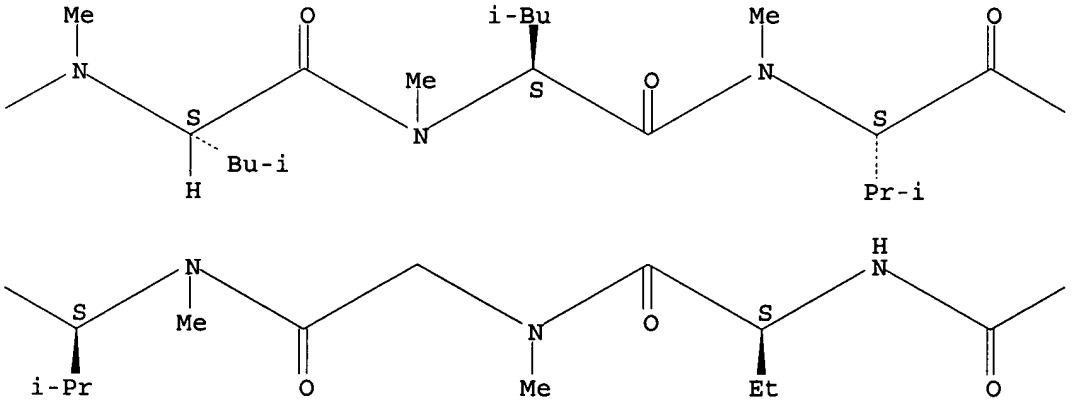
RELATED SEQUENCES AVAILABLE WITH SEQLINK

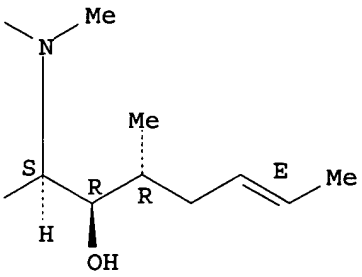
Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B





RELATED SEQUENCES AVAILABLE WITH SEQLINK

REFERENCE 1: 144:164275

REFERENCE 2: 141:296284

REFERENCE 3: 140:53021

REFERENCE 4: 137:362480

REFERENCE 5: 137:345609

REFERENCE 6: 134:371585

REFERENCE 7: 134:65905

REFERENCE 8: 132:88163

REFERENCE 9: 132:18781

REFERENCE 10: 129:339480

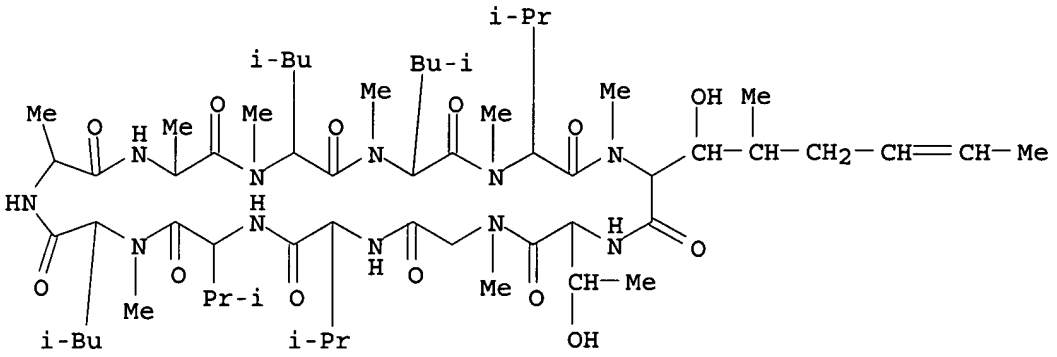
L23 ANSWER 5 OF 6 REGISTRY COPYRIGHT 2006 ACS on STN
RN 108027-43-6 REGISTRY
CN Cyclosporin S (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1,4,7,10,13,16,19,22,25,28,31-Undecaazacyclotritriacontane, cyclic peptide deriv.
CN Cyclosporin A, 7-L-threonine-9-L-valine-
OTHER NAMES:
CN Cyclo[L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl-(3R,4R,6E)-6,7-didehydro-3-hydroxy-N,4-dimethyl-L-2-aminooctanoyl-L-threonyl-N-methylglycyl-L-valyl-L-valyl-N-methyl-L-leucyl]
NTE cyclic
modified (modifications unspecified)

type	------ location ------		description
uncommon	Aaa-1	-	-
stereo	Ala-8	-	D

SQL 11

SEQ3 1 Aaa-Thr-Gly-Val-Val-Leu-Ala-Ala-Leu-Leu-
11 Val

RELATED SEQUENCES AVAILABLE WITH SEQLINK



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

RELATED SEQUENCES AVAILABLE WITH SEQLINK

REFERENCE 1: 143:466194

REFERENCE 2: 142:120497

REFERENCE 3: 140:133858

REFERENCE 4: 138:221831

REFERENCE 5: 137:362480

REFERENCE 6: 137:345609

REFERENCE 7: 134:344591

REFERENCE 8: 134:223185

REFERENCE 9: 132:251583

REFERENCE 10: 130:306591

L23 ANSWER 6 OF 6 REGISTRY COPYRIGHT 2006 ACS on STN
RN 108027-42-5 REGISTRY
CN Cyclosporin Q (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1,4,7,10,13,16,19,22,25,28,31-Undecaazacyclotritriacontane, cyclic peptide deriv.
CN Cyclosporin A, 9-L-valine-
OTHER NAMES:
CN Cyclo[L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-

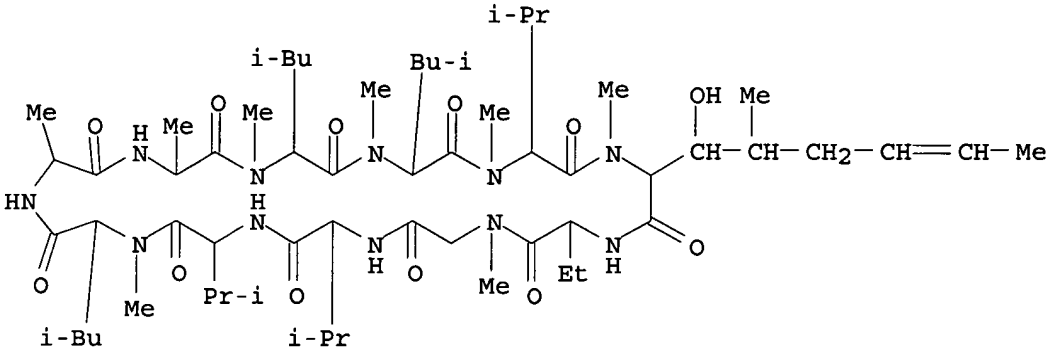
valyl-(3R,4R,6E)-6,7-didehydro-3-hydroxy-N,4-dimethyl-L-2-aminooctanoyl-L-2-aminobutanoyl-N-methylglycyl-L-valyl-L-valyl-N-methyl-L-leucyl]

NTE cyclic
modified

type	location		description
uncommon	Aaa-1	-	-
uncommon	Abu-2	-	-
stereo	Ala-8	-	D

SQL 11

SEQ3 1 Aaa-Abu-Gly-Val-Val-Leu-Ala-Ala-Leu-Leu-
11 Val



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

REFERENCE 1: 143:466194

REFERENCE 2: 137:362480

REFERENCE 3: 137:345609

REFERENCE 4: 135:257447

REFERENCE 5: 134:344591

REFERENCE 6: 130:306591

REFERENCE 7: 130:43304

REFERENCE 8: 117:248314

REFERENCE 9: 112:4323

REFERENCE 10: 106:210631

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